# MOLNUPIRAVIR
## FOR THE TREATMENT OF COVID-19

## INFORMATION FOR HEALTH PROFESSIONALS

Washington, D.C., June 2022

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Food and Agriculture Organization of the United Nations
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This publication is a compilation of information and recommendations for the use of molnupiravir for the treatment of COVID-19, based on the available literature.

## DESCRIPTION

Molnupiravir is an oral medication that facilitates its outpatient use, with broad activity against viruses containing ribonucleic acid (RNA); it significantly inhibits the replication of SARS-CoV-2 and its potency in vitro is similar to that of remdesivir (*1*, *2*). It is indicated in patients with a positive SARS-CoV-2 test who have mild or moderate (not severe) COVID-19, but who have significant risk factors associated with an increased likelihood of progression to severe or critical COVID-19 (hospitalization or death) (*3*).

**Molnupiravir should not be used as a substitute for COVID-19 vaccination or as a preventive treatment for SARS-CoV-2 infection. Its use has been approved by some national regulatory authorities for medicines at the international level (see references).**

## MECHANISM OF ACTION

Molnupiravir is a prodrug that rapidly converts to the ribonucleoside β-D-N4-hydroxycytidine (NHC) in plasma. NHC is distributed in cells and the enzyme kinase transforms it into ribonucleoside triphosphate (NHC-TP), which is pharmacologically active; viral RNA polymerase incorporates it into the viral genome, resulting in an accumulation of errors that leads to the inhibition of viral replication. This mechanism of action is known as viral error catastrophe (*4*).

# INDICATIONS

Molnupiravir is indicated for the treatment of mild or moderate (non-severe or non-critical) COVID-19 in patients with the following characteristics:

- Age 18 years or older.
- Confirmed positive COVID-19 diagnosis.
- At increased risk of hospitalization or death.
- Within 5 days of symptom onset.
- Lack access to alternative or clinically appropriate antiviral treatments (*1*, *2*).

Patients at increased risk of hospitalization or death from COVID-19 include (*3*):

- Immunocompromised individuals who are not expected to mount an adequate immune response to the COVID-19 vaccine or to infection with SARS-CoV-2, regardless of vaccination status.
- Unvaccinated individuals aged 75 years or older.
- Individuals aged 65 years or older with additional clinical risk factors, i.e., presence of two or more comorbidities, hypertension, obesity (body mass index >30), diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, cerebrovascular disease, thrombocytopenia, active smokers, and cancer.

## LIMITATIONS ON USE (*1*, *2*, *5*)

**Molnupiravir should NOT be used in the following cases:**

- **Patients with severe or critical COVID-19.**
- **Patients who have had symptoms for more than 5 days.**
- **Children and adolescents (under 18 years old).**
- **Pregnant or breastfeeding people.**
- **Once the drug has been administered for 5 consecutive days.**

# DURATION OF TREATMENT

The **duration of treatment with molnupiravir is 5 days**. Patients should be instructed not to interrupt the course of treatment until it is completed (even if they feel improvement) in order to prevent the development of antiviral resistance and loss of drug efficacy at the population level (*1*, *2*).

## ADVERSE REACTIONS

The most common adverse reactions in the molnupiravir treatment group in the MOVe-OUT trial were diarrhea (2%), nausea (1%), and dizziness (1%), all grade 1 (mild) or 2 (moderate) (*5*). Serious adverse events, which occurred in 7% of patients receiving molnupiravir, were related to COVID-19 and not to the drug (*4*, *6*).

## CONTRAINDICATIONS

The use of molnupiravir is contraindicated in patients with hypersensitivity or allergy to this active substance or any of the excipients (*4*, *6*).

# Warnings and special precautions

### Use during pregnancy

**There are currently no human data available on the safety of molnupiravir during pregnancy. Although COVID-19 poses a significant risk to both the pregnant person and the fetus, its mechanism of action and preclinical data in animals justify a cautious approach; therefore, it is recommended to avoid its use during pregnancy (*1*, *2*).**

**However, in the case of pregnant people with COVID-19 who are at high risk of developing severe disease, when other treatments are not available and embryogenesis has already occurred (more than 10 weeks of gestation), the use of molnupiravir could be considered once the potential risks have been assessed and provided that the patient knows about the risks and expresses their agreement (*4*, *7*).**

## Use when breastfeeding

**It is unknown whether the administration of molnupiravir during the lactation period can cause adverse effects in infants through breastmilk. Therefore, breastfeeding should be discontinued during treatment with molnupiravir and for 4 days following the final dose (*1*, *2*, *5*).**

## Use in pediatric patients

**The efficacy and safety of molnupiravir have not been evaluated in children under 18 years of age. Due to the potential effects on bone and cartilage growth, its use in this age group is not recommended (*1*, *2*, *5*).**

## Use in people of reproductive age

**For women and other people with a female reproductive system, a pregnancy test is recommended before starting treatment with molnupiravir (*3*). It is advisable that they abstain from sexual intercourse or, alternatively, use reliable contraceptive methods during treatment and for up to 4 days after receiving the last dose of molnupiravir (*1*, *2*, *5*). In the case of penetrative sex with a sexual partner who is currently receiving treatment with molnupiravir or was treated recently, it is recommended to use a reliable contraceptive method for 3 months following completion of the last dose of the drug (*1*, *2*).**

**Men and other people with a male reproductive system should be informed about the potential temporary genotoxic effect of molnupiravir on sperm production (*1*, *2*). They should abstain from penetrative sex or use reliable contraceptive methods during treatment and until at least 3 months after receiving the last dose of molnupiravir (*1*, *2*, *5*).**

**The potential risk of long-term genotoxicity may be higher in younger versus older patients; therefore, use in young adults who are not at high risk of developing severe disease should be limited (*1*, *2*).**

## DOSE

Treatment with molnupiravir should be started within 5 days of onset of COVID-19 symptoms. **The recommended dose is 800 mg every 12 hours for 5 days**, which can be taken with or without food. No dose adjustment is required in patients with renal or hepatic impairment, or in those over 65 years of age (*1*, *2*, *4*, *5*).

It is recommended that the patient swallow the molnupiravir capsules whole; but in cases where this is not possible and alternative treatments are not available, an oral solution may be prepared (*5*) (see preparation instructions at the end of this publication).

In the **case of a missed dose** within 10 hours after the usual time, the patient should take the respective dose as soon as possible, and the next dose at the usual time. If more than 10 hours have passed, the patient should not take the missed dose and should wait for the time corresponding to the next dose. Double doses should not be taken to compensate for missed doses (*1*, *2*).

## DRUG INTERACTIONS

To date, no drug interactions with molnupiravir have been identified (*1*). The prodrug molnupiravir and NHC are not inhibitors or inducers of the major mechanisms of metabolization of drugs, enzymes, or transporters; therefore, a potential interaction between molnupiravir or NHC and concomitant medications is considered unlikely (*1*, *2*, *4*, *5*).

To verify specific interactions between molnupiravir and other medicines or classes of medicines, it is recommended to use the University of Liverpool's COVID-19 drug interactions checker: https://www.covid19-druginteractions.org/checker.

## CONSERVATION

Store the medicinal product in its original packaging, at a temperature between 2 °C and 25 °C (68 °F to 77 °F) (*7*) and not above 30 °C (86 °F) (*5*), and away from heat, light, and moisture (*4–6*, *9*).

# EFFICACY

The benefit of using molnupiravir in patients at increased risk of hospitalization or death has been estimated at 60 fewer hospitalizations per every 1,000 patients, with a greater expected benefit of absolute survival (although the latter has not yet been quantified due to lack of data) (*1*, *2*).

The efficacy and safety of molnupiravir were evaluated in a phase III, randomized, placebo-controlled, double-blind clinical trial called MOVe-OUT, which included 1433 unvaccinated participants with a median age of 43 years (*4*, *6*, *9*). In this study, the rate of hospitalization or death through day 29 was approximately 31% lower with molnupiravir than with the placebo (hazard ratio (HR): 0.69; 95% confidence interval (CI): 0.48 to 1.01). One death was reported in the molnupiravir group (all-cause mortality at 29 days: 0.1%) and 9 deaths were reported in the placebo group (all-cause mortality at 29 days: 1.3%); the risk of death was 89% lower (95% CI: 14 to 99) with molnupiravir than with the placebo (*10*).

Administration of molnupiravir at doses of 800 mg every 12 hours to patients who initiated treatment within 5 days of symptom onset provided a statistically significant reduction in the rate of hospitalization or death (*6*).

## Efficacy against variants of concern

Molnupiravir demonstrated activity against alpha and beta variants in in vivo assays, and against delta and omicron variants in in vitro assays. Data on in vivo activity against delta or omicron variants are currently unavailable (*1*, *2*). There are also insufficient data to determine the potential resistance of SARS-CoV-2 to molnupiravir. Although there appears to be no molecular basis for loss of activity, there is residual uncertainty about whether a higher rate of replication or transmission may affect the efficacy of the drug (*1*, *2*).

Drug resistance appears through the inherent variability in viral sequences that occur spontaneously as the virus replicates; some of them exert selective pressure that gives the virus survival advantages in the presence of the drug. It has been found that there may be an increased risk of resistance in immunocompromised patients due to longer replication of the virus in this group. There may also be an increased risk of resistance in patients with poor adherence to treatment, in whom suboptimal concentrations of the drug occur (*1*, *2*, *4*, *5*).

## EMERGENCE OF NEW VARIANTS

There is a possibility that random mutagenesis resulting from molnupiravir's mechanism of action increases the diversity of viral sequences and, therefore, the faster emergence of new variants of SARS-COV-2 (*1*, *2*).

In the clinical trials conducted, a higher rate of SARS-COV-2 mutation was observed in patients treated with molnupiravir compared to patients who received the placebo, in terms of nucleotide changes in viral RNA and their translation into amino acid changes. The clinical relevance of this finding, which is part of the follow-up on the use of monulpiravir that should be implemented, has not yet been determined (*5*).

## SAFETY

Safety data for molnupiravir are limited, both in individual patients and at the population level. In addition, long-term risks related to genotoxicity, emergence of resistance, and emergence of new variants remain unknown (*1*, *2*).

As a mutagenic ribonucleoside antiviral, there is a theoretical risk that molnupiravir will be metabolized by the human cell and incorporated into the DNA, which could lead to mutations. However, based on the results of the genotoxicity studies available to date and the treatment duration of 5 days, it has been established that the risk of genotoxicity for molnupiravir is low.

With regard to the potential effects of molnupiravir on bone marrow, there appears to be no clinical evidence of this effect when treatment is limited to 800 mg every 12 hours for up to 5 days (*1*, *2*, *4–7*).

## PHARMACOVIGILANCE

Molnupiravir is a newly authorized medication. For this reason, more safety data are needed from post-authorization studies and active pharmacovigilance to supplement the safety information that is currently available (*1*, *2*).

Health personnel should document all suspected adverse reactions in treated patients and report them to the national pharmacovigilance system (*1–3*). For more information on surveillance in the WHO protocol for safety monitoring of molnupiravir, refer to the following link: https://www.who.int/publications/i/item/WHO-2019-nCoV-Therapeutics-safety_monitoring-molnupiravir-2022.1.

# PRECLINICAL TOXICITY

In studies conducted in developing rats, an increase in the thickness of the growth plate associated with decreased bone formation was observed. Therefore, molnupiravir should not be given to pediatric patients (*1*, *2*).

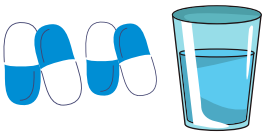
In the offspring of pregnant animals receiving molnupiravir, embryo-fetal lethality and teratogenicity were observed; therefore, molnupiravir should not be administered to pregnant or breastfeeding people. In addition, low concentrations of NHC were detected in 10-day-old rat pups, suggesting that NHC may be present in breast milk; therefore, molnupiravir should not be given to people who are breastfeeding (*1*, *2*, *4*–*6*).

There is a lack of data on the effect of molnupiravir on spermatogenesis, in order to quantify the risks to the embryo or fetus conceived by parents who are receiving or recently received molnupiravir (*1*, *2*, *7*).

Genetic toxicology data demonstrated that molnupiravir is mutagenic in vitro, but there is no evidence of mutagenicity in animal models. It is unknown whether it may be carcinogenic in humans (*1*, *2*).

# ANNEX

## PREPARATION OF AN ORAL SOLUTION OF MOLNUPIRAVIR



The recommendation is to swallow molnupiravir capsules; if the patient cannot swallow the capsules and alternative treatments are not available, an oral solution can be prepared, according to the following instructions (*5*):

- Open the four 200 mg capsules (equivalent to the dose of 800 mg) and transfer the contents to a container or syringe.
- Add approximately 40 ml of water to the container or syringe.
- Dissolve the contents of the capsules in the water by stirring it for 3 minutes. The insoluble contents of the capsules may not be completely diluted and whole particles may be observed in the prepared solution; they can be administered orally.
- This preparation should be administered as soon as possible, within a maximum period of 2 hours. Prior to administration, the solution should be mixed for 1 minute to attain the suspension again.
- The oral solution should be administered while using personal protective equipment, in accordance with local regulations.
- For the disposal of hazardous or biohazardous wastes, local procedures should be followed.
- Wash hands after providing the dose.

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PAHO/HSS/MT/COVID-19/22-0021

**The purpose of this publication is for health professionals to be aware of the potential benefits and risks of molnupiravir, a medicine to treat COVID-19, so that they can make informed decisions about the treatment of their patients and provide them with the necessary information for its correct use. In addition, it seeks to promote the notification of suspected adverse drug reactions to the national pharmacovigilance system.**

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