To be sold by retail on the prescription of Registered Medical Practitioner only.

PRESCRIBING INFORMATION

Molnupiravir Capsule

GENERIC NAME

Molnupiravir Capsules 200 mg, 400 mg

BRAND NAME

Monovir 200
Monovir 400

QUALITATIVE AND QUANTITATIVE COMPOSITION

Monovir 200

Each capsule contains:
Molnupiravir ..... 200 mg

Approved colours used in empty capsule shell.

Monovir 400

Each capsule contains:
Molnupiravir..... 400 mg

Approved colours used in empty capsule shell.

DOSAGE FORM AND STRENGTH

Oral, Capsule, 200 mg and 400 mg

CLINICAL PARTICULARS

Therapeutic indication

For treatment of patients with mild to moderate COVID-19 disease.

Posology and method of administration

The recommended dosage is as follows:
Adults: Molnupiravir 800 mg (4 capsules of 200 mg/2 capsules of 400mg) administered orally every 12 hours for 5 days

Note: Use only as directed by the Physician

The administration should be started promptly after suspected or laboratory confirmation of SARS CoV-2 infection in adults with mild to moderate disease.

Use in Elderly: Since the elderly often have reduced physiological function, Molnupiravir should be administered with care to them by monitoring their general condition

Use in Children: Molnupiravir has not been administered to children

Contraindications

- Patients with a history of hypersensitivity to the components of this drug
- A pregnant or lactating woman or a woman who may be pregnant
- Patients with severe hepatic impairment
- Patients with severe renal impairment

Special warnings and precautions for use

Warnings

Molnupiravir may be lethal to early embryo as well as to cause teratogenicity and, hence, cannot be administered to a pregnant woman or a woman suspected to be pregnant.

If the drug is to be administered to a woman with a possibility of becoming pregnant, a pregnancy test should be done before starting the drug to confirm negative pregnancy before starting the drug. In addition, the risks should be fully explained, and guidance should be given (to the female patient) accompanied by the partner to ensure implementation of extremely effective contraceptive methods during the administration period and for 7 days after the completion of the administration. Furthermore, if pregnancy is suspected during the administration period of this product, administration should be discontinued immediately, and the patient should be instructed to contact a physician.

When administering to male patients, make sure to fully explain the risks and instruct to use extremely effective contraceptive methods during sexual intercourse during the administration period and up to 7 days after the completion of the administration of the drug (men must wear condoms).

Prior to starting the treatment, patients or their families should be fully explained about the efficacy and risks (including risk of foetal exposure) and this should be documented.

When administering this drug, the necessity of this drug should be carefully considered.

Precautions

Bacterial infections can be associated with influenza virus infection or can be confused with flu-like symptoms. In case of a bacterial infection and if a bacterial infection is suspected, take appropriate measures such as administration of antibacterial agents.

Drugs interactions

There are no known metabolism concerns that are sex- or race-based.

Use in special populations

- Pregnant Women

Molnupiravir should not be administered to a pregnant woman or a woman who may be pregnant.
(In animal studies, early embryonic lethality (rat) and teratogenicity (monkey, mouse, rat, and rabbit) were observed at doses similar to or lower than the clinical trial exposure level.)

- Lactating Women

Do not administer to lactating women.
If administered to a nursing mother, stop the breastfeeding.

- Paediatric Patients

There is no administration experience in children. Safety and efficacy is not established in paediatric population.

- Geriatric Patients

In general, since the physiological functions are often reduced in the elderly, the administration should be done while observing the patient's condition.

Effects on ability to drive and use machines

No data available.

In the case of side effects such as abnormal behaviour or psychiatric symptoms, the patient's ability to concentrate and to react properly may be impaired. In such cases, patients should refrain from driving cars and using machines

Undesirable effects

Molnupiravir was well tolerated at doses of 50 to 800 mg administered two times daily for 5.5 days and at single doses up to 1,600 mg.

- The most frequently observed adverse event was headache in the single-ascending dose part and diarrhea in the multiple ascending dose study.
- Adverse effects like oropharyngeal pain, pain in extremity, influenza-like illness and pruritic rash were also reported in few subjects.
- There were no clinically significant findings or dose-related trends in clinical laboratory, vital signs, and electrocardiogram data. There were no clinically significant changes in hematological parameters seen in studies.
- No subjects experienced serious adverse events.
- The absence of clinically significant findings or dose-related trends in clinical laboratory, vital signs, and electrocardiography, taken with the tolerability findings, indicate that molnupiravir was generally safe at the dose levels and duration tested in study cohort.
- All Molnupiravir doses were generally well tolerated in ***Phase 2/3 MOVe-IN Study and Phase 3 MOVe-OUT Study.***
- No safety signals of concern were observed, and ***no dose-limiting toxicity was observed at the highest dose (800 mg)***

Phase 3 DRL-MOL-002 study

Safety profile in the interim analysis of the ongoing phase 3 clinical study titled 'A Prospective, Randomized, Multicenter, open label, Parallel Group, Phase III Trial to Evaluate Safety and Efficacy of Oral Molnupiravir as add on to Standard supportive Care for treatment of Mild Patients with COVID-19 Disease.'in a subset of 374 subjects was as follows:

Summary of Treatment Emergent Adverse Events by SOC and PT- Safety Analysis Set

SOC/PT n,(%), E	Molnupiravir 800mg +SOC (N=192)	SOC (N=182)	Overall (N=374)
Total	1(0.5%)	6(3.3%)	7(1.9%)
Eye Disorder	0(0.0%)	1(0.5%)	1(0.3%)
Eye irritation	0(0.0%)	1(0.5%)	1(0.3%)
General disorder and administration site reactions	1(0.5%)	1(0.5%)	2(0.5%)
Chills	0(0.0%)	1(0.5%)	1(0.3%)
Pyrexia	1(0.5%)	0(0.0%)	1(0.3%)
Musculoskeletal and connective tissue disorder	0(0.0%)	2(1.1%)	2(0.5%)
Muscle spasm	0(0.0%)	2(1.1%)	2(0.5%)
Nervous system disorders	0 (0.0%)	1 (0.5%)	1 (0.3%)
Headache	0 (0.0%)	1 (0.5%)	1 (0.3%)
Renal and urinary disorders	0 (0.0%)	1 (0.5%)	1 (0.3%)
Nephrolithiasis	0 (0.0%)	1 (0.5%)	1(0.3%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (0.5%)	1 (0.3%)
Erythema	0 (0.0%)	1 (0.5%)	1 (0.3%)

All reported adverse events were mild in nature. No SAEs or deaths were reported till the interim analysis is conducted.

Reporting of suspected adverse reactions

If you experience any side effects, talk to your doctor or write to drugsafety@cipla.com.

By reporting side effects, you can help provide more information on the safety of this product.

Overdose

No data available on overdosage of this product.

Pharmacological properties

Mechanism of Action

Molnupiravir (also known as EIDD-2801/MK-4482) is a prodrug of the active antiviral ribonucleoside analogue β-d-N4-hydroxycytidine (NHC; EIDD-1931). Molnupiravir is quickly cleaved in plasma to EIDD-1931, which after distribution into various tissues, is converted to its corresponding 5'-triphosphate by host kinases.

EIDD-1931 5'-triphosphate is a competitive alternative substrate for the virally encoded RNA-dependent RNA polymerase, and upon incorporation into nascent chain viral RNA, it induces an antiviral effect via viral error catastrophe, a concept that is predicated on increasing the viral mutation rate beyond a biologically tolerable threshold, resulting in impairment of viral fitness and leading to viral extinction.

Pharmacodynamic properties

Antiviral Activity

Molnupiravir, the prodrug of the active antiviral ribonucleoside analogue b-D-N4-hydroxycytidine which has demonstrated the activity against a number of RNA viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and seasonal and pandemic influenza viruses and encephalitic alphaviruses in nonclinical models.

Resistance

No information about emergence of Molnupiravir-resistant viruses is available.

Pharmacokinetic properties

Single and multiple doses of molnupiravir were evaluated in this first-inhuman, phase 1, randomized, double-blind, placebo-controlled study in healthy volunteers, which included evaluation of the effect of food on pharmacokinetics.

EIDD-1931 appeared rapidly in plasma, with a median time of maximum observed concentration of 1.00 to 1.75 h, and declined with a geometric half-life of approximately 1 h, with a slower elimination phase apparent following multiple doses or higher single doses (7.1 h at the highest dose tested).

Mean maximum observed concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) increased in a dose-proportional manner, and there was no accumulation following multiple doses.

TABLE: Pharmacokinetic parameters of EIDD-1931 (50 to 800 mg molnupiravir, twice-daily multiple ascending doses) (N = 6)

Parameters[a]	Day 1				Day 6			
	50mg	200mg	400mg	800mg	50mg	200mg	400mg	800mg
AUC_t (ng · h/ml)	**461**	1660	3800	8190	432	1730	3710	8330
AUC_{last} (ng · h/ml)	**444**	1640	3790	8180	**414**	1720	3730	8450
C_{max} (ng/ml)	**223**	766	1530	2770	188	742	1470	2970
t_{max} (h)	**1.00**	1.50	1.50	1.75	1.00	1.50	1.50	1.50
$t_{1/2}$ (h)	**0.937**	0.960	1.05	1.18	0.968	1.24	1.20[b]	7.08[d]

[a]Geometric means are presented, with the exception of t_{max}, for which medians (minimum to maximum) are presented.
AUC_t, area under the plasma concentration-time curve during a dosing interval;
AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable nonzero concentration;
C_{max}, maximum observed concentration;
$t_{1/2}$, apparent terminal elimination half-life;
t_{max}, time of the maximum observed concentration.

[b]N = 5
[c]N = 3
[d]N = 4

Absorption

Molnupiravir is well absorbed and the appearance of the parent ribonucleoside analogue, EIDD-1931, in plasma demonstrates linear, dose-proportional pharmacokinetics when administered between doses of 50 and 1,600 mg.

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Food Effect

Although the rate of absorption was slower in the fed state, with lower values of tmax and Cmax and a longer duration of measurable exposure, the extent of absorption (as assessed by AUCinf) was similar for both fed and fasted states. Therefore, the administration of molnupiravir with food is unlikely to have an effect on therapeutic exposure. Molnupiravir was well tolerated.

Metabolism/distribution

Molnupiravir is rapidly converted in the plasma to EIDD-1931 (NHC), which after distribution into various tissues is converted by host kinases into EIDD-1931 59-triphosphate, the active antiviral agent.

No accumulation was observed in the multiple-ascending dose part of this study.

Elimination

Very little molnupiravir or EIDD-1931 was detected in urine, despite the fact that nucleoside analogues as well as natural nucleosides are in general actively secreted by the kidney. This may be the result of metabolism of EIDD-1931 to cytidine and uridine.

Between 0.854% and 3.61% of the dose was excreted in urine as EIDD-1931 on both days 1 and 6, and, similar to single doses, the majority was excreted in the first 4 h post dose.

Molnupiravir was well tolerated in this study, and no subjects experienced serious adverse events. Fewer than half of the subjects reported an adverse event, the incidence of adverse events was higher following administration of placebo, and 93.3% of adverse events were mild. One subject discontinued early due to rash. There were no serious adverse events, and there were no clinically significant findings in clinical laboratory, vital signs, or electrocardiography. Plasma exposures exceeded expected efficacious doses based on scaling from animal models; therefore, dose escalations were discontinued before a maximum tolerated dose was reached

Clinical Efficacy

Phase 2a Study

A Phase 2a randomized, double-blind, placebo-controlled trial was conducted to evaluate the safety, tolerability, and efficacy to eliminate SARS-CoV-2 viral RNA of molnupiravir, in symptomatic, outpatient (at baseline) adults with SARS-CoV-2 infection. 202 patients were enrolled. Preliminary results showed that at day 5, there was a reduction (nominal p=0.001, not controlled for multiplicity) in positive viral culture in subjects who received molnupiravir (all doses) compared to placebo: 0% (0/47) for molnupiravir and 24% (6/25) for placebo.

Phase 2/3 MOVe-IN Study

MOVe-IN (MK-4482-001) is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-site trial evaluating the efficacy, safety, and pharmacokinetics of orally administered molnupiravir in hospitalized participants. The Phase 2 portion of the trial enrolled 304 participants randomized 1:1:1:1 to who received molnupiravir 200 mg, 400 mg, 800 mg or placebo twice daily for 5 days.

The planned interim analysis of data from the Phase 2, dose-finding portion (Part 1) of two ongoing placebo-controlled Phase 2/3 trials evaluating molnupiravir administered twice a day for five days in outpatients (MOVe-OUT) and hospitalized patients (MOVe-IN) with COVID-19, and from a previously completed Phase 2a dose-ranging study in outpatients, the decision has been made to proceed with the Phase 3 portion (Part 2) of MOVe-OUT in outpatients with COVID-19, evaluating the 800 mg dose of molnupiravir twice daily.

Data from MOVe-IN indicate that molnupiravir is unlikely to demonstrate a clinical benefit in hospitalized patients, who generally had a longer duration of symptoms prior to study entry; therefore, the decision has been made not to proceed to Phase 3.

Data from the dose-finding portion of these studies are consistent with the mechanism of action and provide meaningful evidence for the antiviral potential of the 800 mg dose

Phase 3 MOVe-OUT Study

MOVe-OUT is an ongoing Phase 2/3, randomized, placebo-controlled, double-blind, multi-site study evaluating the efficacy, safety and pharmacokinetics of orally administered molnupiravir in non-hospitalized participants with COVID-19 confirmed using polymerase chain reaction. The trial plans to enroll a total of 1850 participants with mild or moderate COVID-19. Results of this study are expected by Aug/Sept 2021.

Phase 3 DRL-MOL-002 study

A Prospective, Randomized, Multicenter, open label, Parallel Group, compared to standard of care Phase III Trial to Evaluate Safety and Efficacy of Oral Molnupiravir as add on to Standard supportive Care for treatment in Mild Patients with COVID-19 Disease. This study plans to enroll 1218 patients.

Interim analysis was conducted when 303 subjects (152 in test arm vs. 151 in SOC arm) were enrolled. Results indicate that Molnupiravir when added to standard of care in the treatment of mild COVID-19 patients, provides clinical improvement in significantly high proportion of patients (P = 0.0399 for 2 point improvement and P = 0.02 for 1 point improvement on 10-point WHO ordinal scale) and offers significantly high viral load reduction (significantly higher rise in CT values in RT-PCR reports, P = 0.0091) as compared to standard of care alone. There have been only 1 hospitalization in the study so far, which was for a subject in standard of care arm. Proportion of subjects with RT-PCR negative results were also high in test arm as compared to standard of care arm.

Nonclinical properties

Animal Toxicology or Pharmacology

Comprehensive nonclinical program is conducted to characterize the safety profile of molnupiravir. This program included assays such as Big Blue and PIG-a designed to provide a robust measure of a drug or chemical's ability to induce mutations *in vivo*. Animals were administered molnupiravir for longer and at higher doses (mg/Kg) than those employed in human studies. The totality of the data from these studies indicates that molnupiravir is not mutagenic or genotoxic in *in vivo* **mammalian systems.**

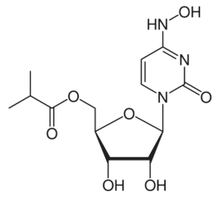
Ferrets were used as an *in vivo* model to examine efficacy of therapeutically administered oral MK-4482/EIDD-2801 against SARS-CoV-2 infection and virus transmission to uninfected contact animals. Viruses were administered to source animals through intranasal inoculation and virus load monitored periodically in nasal lavages and rectal swabs, and 4 or 10 days after exposure in respiratory tissues and a subset of organs. Virus titers were determined based on plaque assay and viral RNA copy numbers, blood samples subjected to CBC analysis and RT-qPCR quantitation of selected cytokine and innate antiviral effector expression levels. Employing the ferret model, study demonstrate high SARS-CoV-2 burden in nasal tissues and secretions that coincides with efficient direct-contact transmission. Therapeutic treatment of infected animals with twice-daily MK-4482/EIDD-2801 significantly reduced upper respiratory tract SARS-CoV-2 load and completely suppressed spread to untreated contact animals. Study identified oral MK-4482/EIDD-2801 as a promising antiviral countermeasure to break SARS-CoV-2 community transmission chains.

Studies with influenza viruses demonstrated that the MK-4482/EIDD-2801-mediated block of respiratory viral transmission is not host species-restricted. Oral treatment with MK-4482/EIDD-2801 or NHC reduced shed influenza virus titers in ferret nasal lavages with potency and kinetics comparable to the effect seen against SARS-CoV-24 and effectively prevented influenza virus direct contact transmission between guinea pigs.

MK-4482/EIDD-28014,5, the orally available pro-drug of the nucleoside analog N4-hydroxycytidine (NHC), has shown potent anti-influenza virus activity in mice, guinea pigs, ferrets, and human airway epithelium organoids.

Description

Molnupiravir (EIDD-2801) is the isopropylester prodrug of [N4-hydroxycytidine].



Molecular Formula: $C_{13}H_{19}N_3O_7$

Molecular Weight: 329.31 g/mol

Chemical name:
[(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl] methyl 2-methylpropanoate

Pharmaceutical particulars

Incompatibilities

Not applicable.

Shelf-life

As on the pack.

Packaging information

Monovir 200 Capsules: Container pack of 40 capsules
Monovir 400 Capsules: Container pack of 20 capsules

Storage and handing instructions
Do not store above 30°C.

Keep out of the reach of children.

Patient Counselling Information

What is Molnupiravir?

Molnupiravir Capsules are a prescription medicine used to treat the following:
Mild to moderate coronavirus 2 (SARS-CoV-2) infection in adults that causes coronavirus disease 2019 (COVID-19).
This drug does not treat bacterial infections.
It should not be used in children.

Who should not take Molnupiravir?

Do not take Molnupiravir Capsules if you are allergic to Molnupiravir or any other ingredient of this Capsule.

You should not be taking Molnupiravir Capsule if you are suffering from severe hepatic impairment (liver failure) or severe renal impairment (kidney failure).

If you are pregnant or lactating/nursing or may be pregnant you should not take Molnupiravir.

Guidance should be given (to the female patient) as well as her partner to ensure implementation of extremely effective contraceptive methods during the administration period and for 7 days after the completion of the administration.

What precautions should I follow when taking Molnupiravir?

Male patients must wear a condom during sexual intercourse during the administration period and up to 7 days after the completion of the administration of the drug.

Female patients must avoid breastfeeding while using this drug.

What should I tell my healthcare provider before taking Molnupiravir?

Before you take Molnupiravir Capsules, tell your healthcare provider if

- you have any other medical condition.
- you are pregnant or planning to become pregnant; and/or
- you are breastfeeding or planning to breastfeed.
- you have kidney disease
- you have liver disease

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Molnupiravir?

Take Molnupiravir Capsules exactly as your healthcare provider tells you to.

What are the possible side effects of Molnupiravir?

The most frequently observed adverse event was headache and diarrhea in studies.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. If you experience any side effects, talk to your doctor or write to drugsafety@cipla.com. By reporting side effects, you can help provide more information on the safety of this product.

How should I store Molnupiravir?
Do not store above 30°C.

Keep Molnupiravir Capsules and all medicines out of the reach of children.

General information about the safe and effective use of Molnupiravir

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Molnupiravir Capsules for a condition for which it was not prescribed. Do not give Molnupiravir Capsules to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider.

Details of manufacturer

Mfd. by
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