WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[CV008 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg molnupiravir

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule

Hard cellulose capsules with an opaque green cap and body. They are printed in white on the cap with 'H' and on the body with 'M11'. They contain white to off white granules.

Note: The capsules are to be swallowed whole. See section 4.2 on 'Method of administration of

[CV008 trade name].

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[CV008 trade name] is indicated for treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe.

This primarily includes patients who have:

- been diagnosed with immunodeficiency syndromes
- undergone solid organ transplantation and are receiving immunosuppressants
- autoimmune illness and are receiving immunosuppressants

Lack of vaccination against SARS-CoV-2 is an additional risk factor.

[CV008 trade name] should only be given when alternative treatment options for these patients are not accessible or not clinically appropriate.

The management of COVID-19 should follow the most recent authoritative guidelines, including those issued by WHO.

4.2 Posology and method of administration

Posology

Treatment with [CV008 trade name] should be started as soon as possible after diagnosing COVID-19 and within 5 days of the onset of COVID-19 symptoms.

The recommended dose of [CV008 trade name] for adults, including the elderly, is 800 mg (4 capsules) by mouth every 12 hours for 5 days.

Missed dose

If the patient does not take a dose of [CV008 trade name] at the right time and:

- the next dose is not due for at least 2 hours, the patient should take the missed dose at once and then take the next dose at the usual scheduled time.
- the next dose is due in less than 2 hours, the patient should skip the missed dose and instead take the next dose at the usual scheduled time.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

The patient should not double the dose to make up for a missed dose.

Children and adolescents

[CV008 trade name] is not indicated for patients aged less than 18 years because its safety and efficacy have not been established (see also section 4.4).

Renal impairment

Dose adjustment is not necessary in patients with renal impairment. Renal function does not appreciably affect elimination of N4-hydroxycytidine (NHC), the active moiety of molnupiravir (see also section 5.2).

Hepatic impairment

Dose adjustment is not necessary in patients with hepatic impairment. NHC, the active moiety of molnupiravir is not expected to be significantly eliminated through the liver (see also section 5.2).

Method of administration

Capsules should be swallowed whole with water. The capsules should not be opened, crushed, or chewed.

[CV008 trade name] can be taken with food or between meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Information on the clinical use of [CV008 trade name] is limited.

Children and adolescents

The growth of bone and cartilage may be affected in children. Bone and cartilage damage occurred in animal studies on molnupiravir. The safety and efficacy of molnupiravir in children and adolescents have not been established in clinical studies.

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 [CV008 trade name] and give appropriate medications and/or supportive care.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the limited data available, no interactions have been identified between molnupiravir and other medicines, including those for treating mild and moderate covid-19. In laboratory studies, neither molnupiravir nor N4-hydroxycytidine (NHC, the active moiety of molnupiravir) induced or inhibited major drug metabolising enzymes or major drug transporting systems. Interactions between [CV008 trade name] and other medicines are therefore considered unlikely.

4.6 Fertility, pregnancy and breastfeeding

Fertility

Data on molnupiravir's effect on human fertility are not available. There were no effects on the fertility of female or male rats at exposures to NHC (the active moiety of molnupiravir) about 2 and 6 times higher, respectively, than in humans receiving the recommended dose (see section 5.3).

Contraception for women and men

Women of childbearing potential must use effective contraception during treatment with [CV008 trade name] and for 4 days afterwards. Since molnupiravir's effect on the efficacy of hormonal contraceptives has not been investigated, barrier methods should be used as a second form of contraception, to avoid pregnancy.

Pregnancy should be ruled out by testing women for pregnancy before starting treatment.

Men should not father a child during treatment with [CV008 trade name] and for 3 months after the last dose since molnupiravir has not been investigated for genotoxic effects on germ cells.

Pregnancy

There is little information on the use of molnupiravir in pregnant women. Teratogenicity and embryolethality occurred in animal studies (see section 5.3).

[CV008 trade name] should not be used during pregnancy unless the woman's clinical condition requires treatment with molnupiravir.

Breast-feeding

It is not known if molnupiravir or any its components appear in human milk, affect milk production, or affect the breastfed infant. Studies in rats have shown presence of molnupiravir in milk (see section 5.3).

Based on the potential for adverse effects on the infant from molnupiravir, breastfeeding should be stopped during [CV008 trade name] treatment and for 4 days after the last dose of [CV008 trade name].

4.7 Effects on ability to drive and use machines

There are no studies on molnupiravir's effects on the ability to drive and use machines. The patient should not drive or undertake skilled tasks if adverse effects such as dizziness occur.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during treatment with molnupiravir and in the 14 days after the last dose were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were mild or moderate.

Tabulated list of adverse reactions

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000).

Nervous system disorders

Common	dizziness, headache

Gastrointestinal disorders

Common	diarrhoea, nausea
Uncommon	vomiting

Skin and subcutaneous tissue disorders

Uncommon	rash, urticaria
Frequency not known	erythema, pruritus

Immune System Disorders

Frequency not known	hypersensitivity, anaphylaxis, angioedema

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is no experience of molnupiravir overdose in humans. Treatment of molnupiravir overdose should consist of general supportive measures including monitoring the patient's clinical status. Haemodialysis is not expected to eliminate NHC (the active moiety of molnupiravir).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05AB18.

Mechanism of action

Molnupiravir is a prodrug that is metabolised to N-hydroxycytidine (NHC), a ribonucleoside analogue. NHC is then phosphorylated in body cells to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). Viral RNA polymerase incorporates NHC-TP into the viral RNA, causing errors to accumulate in the viral genome. These errors inhibit replication of the virus. This mechanism of action is called viral error catastrophe.

Antiviral activity

NHC was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC_{50}) 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), 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 EC_{50} values of 0.55–2.95 µM.

Resistance

No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials of molnupiravir for treating COVID-19. Studies on selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies with other coronaviruses (MHV and MERS-CoV) showed low likelihood of developing resistance to NHC. Following 30 passages in cell culture, susceptibility decreased only a 2-fold and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely in viral sequences in people treated with molnupiravir compared to placebo. In a few people amino acid changes occurred in the spike protein at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

In laboratory studies, NHC retained activity against SARS-CoV-2 and recombinant mouse hepatitis virus with polymerase substitutions (e.g. F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

Clinical efficacy and safety

Evidence on molnupiravir's efficacy is based on data from 1,433 patients in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomised, placebo-controlled, double-blind clinical trial on molnupiravir for treating non-hospitalised patients with mild or moderate COVID-19 who are at risk of their disease progressing to severe COVID-19 or hospitalisation. Patients entered into the study were aged 18 years or older and had one or more of the following risk factors for disease progression: age over 60 years; diabetes; obesity (BMI $\geq$ 30 kg/m^2); chronic kidney disease; serious heart condition; chronic obstructive pulmonary disease; or active cancer.

The study included patients not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days before randomisation. Patients were randomised to receive molnupiravir 800 mg or placebo twice daily for 5 days.

Of 792 patients with 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.

The following table summarises results of the study

Outcome	**Molnupiravir** (709 patients)	**Placebo** (699 patients)	**Adjusted risk difference (95% CI)**
All-cause hospitalisation ≥24 hours for acute care or death within 29 days	6.8%	9.7%	- 3.0% (- 5.9%, - 0.1%)
All-cause mortality within 29 days	0.1%	1.3%	

5.2 Pharmacokinetic properties

The absorption characteristics of [CV008 trade name] have been determined after administration of single capsules of [CV008 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** arithmetic mean ± SD
	N-hydroxycytidine
Maximum concentration (C_{max}) ng/mL	1510 ± 424
Area under the curve (AUC_{0-inf}), a measure of the extent of absorption ng·hour/mL	3402 ± 765
Time to attain maximum concentration (t_{max}) hour	1.54 ± 0.58

Pharmacokinetics of molnupiravir

General	Molnupiravir is a prodrug and is hydrolysed during or after absorption to N4-hydroxycytidine (NHC).
Absorption	Following administration of molnupiravir 800 mg twice daily, the median time to peak plasma NHC concentration (T_{max}) was 1.5 hours. Concomitant intake with food does not affect the AUC but decreased C_{max} by 35%.
Distribution	
Volume of distribution (mean)	142 L
Plasma protein binding in vitro	0%
Metabolism	NHC is metabolised to uridine or cytidine (or both) through pathways involved in the metabolism of endogenous pyrimidine
Elimination	
Effective half life	3.3 hours
Apparent clearance	76.9 L/hour
Proportion of dose excreted in urine over 12 hours	≤ 3%

Drug interactions	Molnupiravir and NHC are not considered to be substrates of CYP enzymes or P-gp and BCRP transporters. Studies also indicate 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.

Renal impairment

Renal clearance is a minor elimination pathway for NHC. In a population pharmacokinetic analysis, mild or moderate renal impairment had little effect on the pharmacokinetics of NHC. The pharmacokinetics of molnupiravir and NHC have not been evaluated in patients with eGFR less than 30 mL/minute/1.73m^2 or on dialysis.

Hepatic impairment

The pharmacokinetics of molnupiravir and NHC have not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicates that hepatic elimination is not a major route for eliminating NHC; therefore, hepatic impairment is unlikely to affect NHC exposure.

Gender, race, and age

Population pharmacokinetic analysis showed that age, gender, race and ethnicity do not meaningfully influence the pharmacokinetics of NHC.

Paediatrics

Molnupiravir has not been studied in children and adolescents.

5.3 Preclinical safety data

General toxicity

Reversible, dose-related bone marrow toxicity affected all haematopoietic cell lines in dogs in a 28-day study at ≥ 0.4 times expected human NHC exposure at the recommended dose. Peripheral blood cell and platelet counts decreased mildly after 7 days of molnupiravir treatment, progressing to more severe haematological changes after 14 days of treatment.

In a 3-month study, bone and cartilage toxicity – consisting of increased thickness of physeal and epiphyseal growth cartilage with decreased trabecular bone in the femur and tibia – occurred in rapidly growing rats at ≥ 5.4 times the expected human NHC exposure with the recommended dose. Growth cartilage is not present in mature skeletons; therefore, the bone and cartilage findings are not relevant for adult patients. The clinical significance of these findings for children and adolescents is unknown.

Carcinogenesis

Carcinogenicity studies in mice do not indicate carcinogenic potential of molnupiravir.

Genotoxicity

Molnupiravir and NHC were positive in the bacterial reverse mutation assay (Ames assay) with and without metabolic activation. A Pig-a in vivo mutagenicity assay was considered equivocal; findings with molnupiravir treatment compared to controls were statistically significant but these values were within the range of historical control data. In an in vivo transgenic rodent mutagenicity assay, molnupiravir was negative and did not increase mutation rates. Molnupiravir was negative for induction of chromosomal damage in in vitro micronucleus (with and without metabolic activation) and in vivo rat micronucleus assays.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Reproductive toxicity

There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures, respectively, about 2 and 6 times the human NHC exposure at the recommended dose.

In a study in rats, molnupiravir administered orally to pregnant rats resulted in developmental toxicity including post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at exposures 7.5 times the human NHC exposure at the recommended dose. Decreased fetal weight and delayed ossification were seen at exposures 2.9 times the human NHC exposure at the recommended dose. There was no developmental toxicity at exposures 0.8 times the human NHC exposure at the recommended dose. Maternal toxicity included decreased food consumption and body weight losses, resulting in the early sacrifice of individual animals at exposures 7.5 times the human NHC exposure at the recommended dose, and decreased body weight gain at exposures 2.9 times the human NHC exposure at the recommended dose.

Molnupiravir administered orally to pregnant rabbits resulted in reduced fetal weight at exposures 18 times the human NHC exposures at the recommended dose. There was no developmental toxicity at exposures 6.5 times the human NHC exposures at the recommended dose. Maternal toxicity included reduced food consumption and body weight gain, and abnormal faecal output at exposures 18 times the human NHC exposures at the recommended dose.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats from gestation day 6 to lactation day 20 at exposures up to 1.6 times the human NHC exposures at the recommended dose. No effects were seen in the offspring. Toxicokinetics in the offspring on postnatal day 10 suggested the presence of molnupiravir in the milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: microcrystalline cellulose
hydroxypropyl cellulose
croscarmellose sodium
magnesium stearate

Capsule shell: gelatin
iron oxide yellow
titanium dioxide
FD&C blue #2/indigo carmine
hypromellose
carrageenan
potassium acetate

Printing ink: shellac
propylene glycol
potassium hydroxide
titanium dioxide

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per capsule.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

HDPE bottle

Opaque white plastic (HDPE) bottle containing 40 capsules. It contains a sachet of desiccant (drying material) and a piece of rayon wool to keep the capsules in place. The bottle has an opaque plastic (polypropylene) screw cap with pulp liner.

Blister

Alu-Alu blister card, each containing 10 capsules. Available in cartons of 4 x 10 capsules.

6.6 Special precautions for disposal and other handling

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

CV008

9. DATE OF PREQUALIFICATION

21 September 2022

10. DATE OF REVISION OF THE TEXT

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References

General

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Section 4.6 and 5.3

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Molnupiravir - Drugs and Lactation Database (LactMed) - NCBI Bookshelf (nih.gov) Available at: https://www.ncbi.nlm.nih.gov/books/NBK501547 [Accessed 17 Sep 2022]

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products