SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MOLNUPIRAVIR 200 DRL Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of molnupiravir

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

White to off white powder filled in white to off white opaque coloured empty hypromellose capsules without imprinting.

The capsule shell size is '0'.

The dimension of the capsule is:

Body length: 18,10 mm to 18,90 mm

Cap length: 10,30 mm to 11,10 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOLNUPIRAVIR 200 DRL capsules is indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test, who do not require supplemental oxygen due to COVID-19 and who have at least one risk factor for developing severe illness (see section 5.1 Clinical Studies).

4.2 Posology and method of administration

Posology:

The recommended dosage is as follows:

Adults: 800 mg (four (4) capsules of 200 mg) administered orally every 12 hours for 5 days.

Should a patient require hospitalisation after starting treatment with MOLNUPIRAVIR 200 DRL, the patient may complete the full 5-day treatment course per the healthcare provider's discretion.

The safety and efficacy of molnupiravir, as in MOLNUPIRAVIR 200 DRL, when administered for periods longer than 5 days have not been established.

MOLNUPIRAVIR 200 DRL should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset in adults who are at risk for progression to severe COVID-19, including hospitalisation or death. Certain medical conditions or other factors may place individual patients at increased risk for progression to severe COVID-19 (see section 5.1 Clinical Studies).

Missed dose

If the patient misses a dose of MOLNUPIRAVIR 200 DRL within 10 hours of the time it is usually taken, the patient should take as soon as possible and resume the normal dosing schedule. If a 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.

Special Populations

Elderly

No dose adjustment of MOLNUPIRAVIR 200 DRL is required based on age (see section 5.2 Gender, Race and Age).

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2 Hepatic Impairment).

Renal impairment

The pharmacokinetics of molnupiravir, as in MOLNUPIRAVIR 200 DRL, and n-hydroxycytidine (NHC) has not been evaluated in patients with eGFR less than 30 mL/min or on dialysis.

Method of administration

MOLNUPIRAVIR 200 DRL is given orally with or without food.

The capsules should be swallowed whole with a sufficient amount of fluid (e.g., a glass of

water). The capsules should not be opened, crushed or chewed

4.3 Contraindications

- Hypersensitivity to the active substance, molnupiravir, or to any of the excipients of MOLNUPIRAVIR 200 DRL listed in section 6.1.

4.4 Special warnings and precautions for use

None.

Sodium

MOLNUPIRAVIR 200 DRL contains less than 1 mmol sodium (23 mg) per dose of 4 capsules, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

No drug interactions have been identified based on the limited available data. Clinical drug-drug interaction trials of MOLNUPIRAVIR 200 DRL with concomitant medications have not been conducted. Molnupiravir is hydrolysed to NHC prior to reaching systemic circulation.

Uptake and metabolism of NHC are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major drug metabolising enzymes or transporters. Neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or transporters. Therefore, the potential for molnupiravir or

NHC to interact with concomitant medications is considered unlikely**.**

4.6 Fertility, pregnancy and lactation

Pregnancy

Advise women of childbearing potential to use effective contraception for the duration of treatment and for 4 days after the last dose of MOLNUPIRAVIR 200 DRL.

Risk Summary

Based on animal data, molnupiravir, as in MOLNUPIRAVIR 200 DRL, may cause foetal harm when administered to pregnant women. There are no available data on the use of molnupiravir, as in MOLNUPIRAVIR 200 DRL, in pregnant women to evaluate the risk of major birth defects, miscarriage or adverse maternal or foetal outcomes. The use of MOLNUPIRAVIR 200 DRL is not recommended during pregnancy. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofoetal lethality and teratogenicity at 8 times the human NHC exposures at the recommended human dose (RHD) and reduced foetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to rabbits during the period of organogenesis resulted in reduced foetal body weights at 18 times the human NHC exposure at the RHD (see section 5.3 Development). In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (1,6 times the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

Breastfeeding

It is unknown whether molnupiravir, as in MOLNUPIRAVIR 200 DRL, or any of the components of molnupiravir are present in human milk, affect human milk production, or have effect on the breastfed infant. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir.

Based on the potential for adverse reactions on the infant from MOLNUPIRAVIR 200 DRL, breastfeeding is not recommended during treatment and for 4 days after the last dose of MOLNUPIRAVIR 200 DRL.

Fertility

There were no effects on female or male fertility in rats at NHC exposures approximately 2 and 6 times respectively, the exposure in humans at the recommended human dose (RHD) (see section 5.3).

4.7 Effects on ability to drive and use machines

MOLNUPIRAVIR 200 DRL may cause dizziness which may lead to impairment of the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions in patients treated with 800 mg molnupiravir every 12 hours for 5 days in a Phase 3 clinical trial were diarrhoea (2 %), nausea (1 %), and dizziness (1 %) all of which were Grade 1 (mild) or Grade 2 (moderate) in severity.

Tabulated list of adverse reactions

The adverse reactions are listed below by MedDRA system organ class.

Table 1: Tabulated list of adverse reactions

System organ class	Frequency	Adverse Reaction
Immune System Disorders	Less frequent	Hypersensitivity, angioedema
Nervous system disorders	Frequent	Dizziness, headache
Gastrointestinal disorders	Frequent	Diarrhoea, nausea
	Less frequent	Vomiting
Skin and subcutaneous tissue disorders	Less frequent	Erythema, rash, urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It

allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no human experience of overdosage with MOLNUPIRAVIR 200 DRL. Treatment of overdose with MOLNUPIRAVIR 200 DRL should consist of general supportive measures including the monitoring of the clinical status of the patient. Haemodialysis is not expected to result in effective elimination of NHC.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: not yet assigned

The relationship between NHC and intracellular NHC-triphosphate (TP) with antiviral efficacy has not been evaluated clinically.

Mechanism of action

Molnupiravir is a prodrug that is metabolized to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHCTP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the

viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

Microbiology

Antiviral Activity

NHC was active in cell culture assays against SARS-CoV-2 with 50 % effective concentrations (EC50) 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 B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with EC50 values of 1,59; 1,77 and 1,32 and 1,68 µM, respectively. No impact was observed on the *in vitro* antiviral activity of NHC against SARS-CoV-2 when NHC was tested in combination with abacavir, emtricitabine, hydroxychloroquine, lamivudine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir.

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 vitro*

against virus with polymerase substitutions (e.g., F480L, V557L and E802D) associated

with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

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. In mice, molnupiravir significantly reduced infectious SARS-CoV-2 levels in infected transplanted human lung tissue. In SARSCoV- 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.

Clinical Studies

Clinical data are based on data from randomised subjects in the Phase 3 trial which is a randomised, placebo-controlled, double-blind clinical trial studying molnupiravir for the treatment of non-hospitalised patients with mild to moderate COVID-19 who were at risk for progressing to severe COVID-19 and/or hospitalisation. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: 60 years of age or older, 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 enrolment. Subjects were randomised 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

At baseline, in all randomised subjects, the median age was 43 years (range: 18 to 90 years); 17 % of subjects were 60 years of age or older and 3 % were over 75 years of age; 49 % of subjects were male; 57 % were White, 5 % Black or African American, 3 % Asian; 50 % were Hispanic or Latino. 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 %), 60 years of age or older (17 %), and diabetes (16 %). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Efficacy results were consistent across sub-groups including age (>60 years), at risk medical conditions (e.g., obesity, diabetes) and SARS-CoV-2 variants.

Higher percentages of subjects reported sustained improvement or resolution in most self-reported COVID-19 signs and symptoms, as recorded on a daily symptom diary, in the molnupiravir group compared to the placebo group.

5.2 Pharmacokinetic properties

General Introduction

Molnupiravir is a 5´-isobutyrate prodrug that is hydrolysed to NHC prior to reaching systemic circulation. The pharmacokinetics of NHC are similar in healthy subjects and patients with COVID-19.

The pharmacokinetics of NHC at steady-state following administration of 800 mg

molnupiravir every 12 hours are provided below in Table 3.

Table 3: Pharmacokinetics of NHC after administration of 800 mg molnupiravir every 12 hours

NHC Geometric Mean (%CV)		
$AUC_{0\text{-}12hr}$ (ng×hr/mL)*	**C_{max} (ng/mL) †**	**C_{12hr} (ng/mL)***
8260 (41,0)	2970 (16,8)	31,1 (124)
%CV: Geometric coefficient of variation. * Values were obtained from population pharmacokinetics (PK) analysis. †Values were obtained from a Phase 1 study of healthy subjects.		

Absorption

Following twice daily oral administration of 800 mg molnupiravir, the median time to peak plasma NHC concentrations (T_{max}) was 1,5 hours.

Effect of Food on Oral Absorption

In healthy subjects, the administration of a single 200 mg dose of molnupiravir with a high-fat meal had no significant effect on NHC AUC and resulted in a 35 % reduction in NHC peak concentrations (C_{max}). Molnupiravir can be taken with or without food.

Distribution

NHC does not bind to plasma proteins.

Elimination

The effective half-life of NHC is approximately 3,3 hours. The fraction of dose excreted as NHC in the urine was ≤ 3 % in healthy participants.

Special populations:

Gender, Race, Age

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

Paediatric Patients

The pharmacokinetics of molnupiravir in paediatric patients less than 18 years of age have not been evaluated.

Renal impairment

Renal clearance is not a meaningful route of elimination for NHC. No dose adjustment in patients with any degree of renal impairment is needed. In a population pharmacokinetics analysis, mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics of NHC.

While the pharmacokinetics of NHC has not been evaluated in patients with eGFR less than 30 ml/min/1,73m^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 section 4.2 Renal impairment).

Hepatic Impairment

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with hepatic impairment. In a population pharmacokinetic analysis, the AUC_{0-12} of NHC was 5 % higher in subjects with mild hepatic impairment, compared to healthy subjects. This

difference is not considered clinically relevant. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination. No dose adjustment in patients with hepatic impairment is needed (see section 4.2 Hepatic impairment).

5.3 Preclinical safety data

General Toxicity

Reversible, dose-related bone marrow toxicity affecting all haematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (0,4 times 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 haematological changes after 14 days of treatment. Neither bone marrow nor haematological 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 (9,3 and 15 times the human NHC exposure at the RHD in females and males, respectively).

Bone and cartilage toxicity, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone was observed in the femur and tibia of rapidly growing rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5,4 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rapidly growing rats up to 500 mg/kg/day (4,2 and 7,8 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 (1,6 times 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. The clinical significance of these findings for paediatric patients is unknown.

Carcinogenesis

Carcinogenicity studies with molnupiravir have not been conducted**.**

Mutagenesis

Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. In 2 distinct *in vivo* rodent mutagenicity models (Pig-a mutagenicity assay and Big Blue® (cII Locus) transgenic rodent assay) molnupiravir did not induce increased mutation rates relative to untreated historical control animals, and therefore is not mutagenic *in vivo*. 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 genotoxicity data, molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use**.**

Reproduction

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.

Development

In an embryofoetal 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 foetal body weights and delayed ossification at ≥500 mg/kg/day (2,9 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (0,8 times the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of individual 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 foetal 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 faecal output at 750 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Croscarmellose sodium

Hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

Capsule shell:

Hydroxypropylmethylcellulose

Purified water

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store at or below 30 ˚C.

Keep the blisters in the carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

MOLNUPIRAVIR 200 DRL is packed in aluminum blisters containing 10,20,30,40, 50 and 60 capsules.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd.

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Morningside

Sandton

2057

8. REGISTRATION NUMBER

56/20.2.8/1109

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 July 2023

10. DATE OF REVISION OF THE TEXT