Module 1.0 Administration Information

Approved Professional Information

SCHEDULING STATUS **S 4**

1 NAME OF THE MEDICINE

MORLIPAR 200 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg molnupiravir.

Sugar-free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

White to off white powder filled in size'2' Hard gelatin capsule with white opaque cap, imprinted with 'S464' in white colour ink inside the gold band and white opaque body imprinted with '200' in white colour ink inside the gold band on body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MORLIPAR (molnupiravir) capsules are 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.

4.2 Posology and method of administration

Posology

Adults

The recommended dose of MORLIPAR in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. Should a patient require hospitalisation after starting treatment with MOLIPAR, the patient may complete the full 5 day treatment course per the healthcare provider’s discretion.

The safety and efficacy of MORLIPAR when administered for periods longer than 5 days have not been established.

MORLIPAR 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.

Missed dose

If the patient misses a dose of MORLIPAR 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 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 Use

No dose adjustment of MORLIPAR is recommended for elderly patients (see section 5.2).

Renal Impairment

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min or on dialysis (see section 5.2).

Hepatic Impairment

No dose adjustment of molnupiravir is recommended for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of MORLIPAR have not been established in patients less than 18 years of age.

Pregnancy

Based on animal data, molnupiravir may cause foetal harm. Human pregnancy data are not available. The use of molnupiravir is not recommended during pregnancy.

Method of administration

For oral use.

MORLIPAR 200 mg capsules can be taken with or without food.

The capsules should be swallowed whole with enough fluid (e.g., a glass of water). The capsules should not be opened, crushed, or chewed.

4.3 Contraindications

Hypersensitivity to the active ingredient, molnupiravir, or to any of the excipients of MORLIPAR listed in section 6.1

4.4 Special warnings and precautions for use

Sodium

This medicinal product 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 medicinal products and other forms of interaction

No medicine interactions have been identified based on the limited available data. Clinical drug-drug interaction studies of molnupiravir with concomitant medications have not been conducted. Molnupiravir is hydrolysed to N-hydroxycytidine (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 medicine metabolising enzymes or transporters. Neither molnupiravir nor NHC are inhibitors or inducers of major medicine metabolising enzymes or inhibitors of major medicine transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

Risk Summary

Based on animal data, molnupiravir may cause foetal harm when administered to pregnant women. There are no available data on the use of molnupiravir in pregnant women to evaluate the risk of major birth defects, miscarriage or adverse maternal or foetal outcomes. The use of molnupiravir is not recommended during pregnancy.

Breast-feeding

It is unknown whether molnupiravir 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 during animal lactation studies.

Based on the potential for adverse reactions on the infant from molnupiravir, breast-feeding is not recommended during treatment and for 4 days after the last dose of Molnupiravir.

Fertility

Animal studies showed 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).

4.7 Effects on ability to drive and use machines

Molnupiravir has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions reported in patients treated with 800 mg molnupiravir every 12 hours for 5 days in clinical trials were diarrhoea, nausea, dizziness, and headache all of which were Grade 1 (mild) or Grade 2 (moderate).

Tabulated summary of adverse reactions

The adverse events are listed below by MedRA system organ class and frequency. Frequencies are defined as follows: Frequent, Less Frequent and Frequency unknown.

Table 1: Tabulated list of adverse reactions

	SOC category	Frequency	Side effect
Immune system disorders		Less frequent	hypersensitivity
Nervous system disorders		Frequent	dizziness, headache
Gastrointestinal disorders		Frequent	diarrhoea, nausea
		Less frequent	vomiting
Skin and subcutaneous tissue disorders		Less frequent	angioedema, 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/wp-content/uploads/2021/11/6.04_ARF1_v6.0_28Oct2021.docx.pdf, or via the SAHPRA portal: https://primaryreporting.who-umc.org/ZA or via the Med Safety App: https://medsafety.sahpra.org.za/.

4.9 Overdose

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. Haemodialysis is not expected to result in effective elimination of NHC.

5 PHARMACOLOGICAL PROPERTIES

20.2.8 Antiviral agents

5.1 Pharmacodynamic properties

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

Mechanism of Action

Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP 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 (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 B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with EC_{50} 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 clinical studies 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 animal studies. 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.

5.2 Pharmacokinetic properties

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.

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 resulted in a 35 % reduction in NHC peak concentrations (C_{max}), AUC was not significantly affected. 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.

Other special populations

Gender, Race, Age

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

Paediatric population

Molnupiravir has not been studied in paediatric patients.

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 PK 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).

Hepatic Impairment

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with moderate or severe 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Microcrystalline cellulose

Povidone

Crospovidone

Colloidal Silicone Dioxide

Magnesium stearate

Hard gelatin capsules shell:

Titanium dioxide

Gelatin

Sodium Lauryl Sulphate

Printing Ink:

Shellac E904

Dehydrated alcohol E1510

Isopropyl alcohol

Butyl alcohol

Propylene glycol E1520

Strong ammonia solution E527

Yellow iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life is 24 months. Store at or below 30 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

40 capsules packed as 4 X 10 Alu/Alu blister packs in cardboard carton

6.6 Special precaution for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd

106 16th Road

Building 2

Midrand,

1686, South Africa

8 REGISTATRATION NUMBER

57/20.2.8/0058

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 July 2023

10 DATE OF REVISION OF THE TEXT

Dosage form and strength: Capsule, Molnupiravir 200 mg