SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Lagevrio® 200 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of molnupiravir.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Swedish Orange, opaque, size 0 (approximately 21.7 mm x 7.6 mm) hard capsule, printed with MSD corporate logo on the cap and “82” on the body in white ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lagevrio is indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness (see sections 4.2 and 5.1 for information on posology and limits of clinical trial population).

4.2 Posology and method of administration

Posology

Adults
The recommended dose of Lagevrio is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days.

The safety and efficacy of molnupiravir when administered for periods longer than 5 days have not been established (see section 5.1).

Lagevrio should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset (see section 5.1).

Missed dose
If the patient misses a dose of Lagevrio 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 Lagevrio is required based on age (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

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

Paediatric population
The safety and efficacy of Lagevrio in patients below 18 years of age have not been established. No data are available (see section 5.1).

Method of administration
For oral use.
Lagevrio 200 mg capsules can be taken 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 or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Hypersensitivity reactions have been reported with Lagevrio (see section 4.8). If signs or symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue Lagevrio and initiate appropriate medications and/or supportive care.

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 drug interactions have been identified based on the limited available data. No clinical interaction studies have been performed with molnupiravir. Molnupiravir is hydrolysed to N4-hydroxycytidine (NHC) prior to reaching systemic circulation. Uptake of NHC and metabolism to NHC-TP are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major drug metabolising enzymes or transporters. Based on *in vitro* studies, neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or inhibitors of major drug transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Lagevrio in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Lagevrio is not recommended during pregnancy. Women of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of Lagevrio (molnupiravir).

Breast-feeding
It is unknown whether molnupiravir or any of the metabolites 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 (see section 5.3).

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

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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of safety profile
Data from a Phase 3 trial of subjects with mild to moderate COVID-19 treated with molnupiravir (n=710), the most common adverse reactions (≥1% of subjects) reported during treatment and during 14 days after the last dose were diarrhoea (2%), nausea (1%) and dizziness (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

Tabulated list of adverse reactions
Adverse reactions in the Phase 3 trial and post marketing experience are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table 1: Tabulated list of adverse reactions

Frequency	**Adverse Reaction**
Immune System Disorders	
Uncommon	hypersensitivity
Nervous system disorders	
Common	dizziness
Uncommon	headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
Uncommon	vomiting
Skin and subcutaneous tissue disorders	
Uncommon	angioedema, erythema, rash, urticaria, pruritus

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Coronavirus Yellow Card Reporting site at https://coronavirus-yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no human experience of overdosage with Lagevrio. Treatment of overdose with Lagevrio 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

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AB18

Mechanism of action

Molnupiravir is a prodrug that is metabolised to the cytidine nucleoside analogue, ribonucleoside analogue N4-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.

Antiviral Activity

NHC was active in cell culture assays against SARS-CoV-2 (USA-WA1/2020 isolate) 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 antiviral activity against SARS-CoV-2 variants, including Alpha (B.1.1.7), Beta (B.1351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B 1.621) and Omicron (BA.1.1.529/BA.1, BA.1.1, BA.2, BA.4, BA.4.6, BA.5, BQ.1.1, HK.3, JN.1, XBB.1, XBB.1.5 and XBB.1.16) with mean EC_{50} values of 0.25-2.95 µM. 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.

Pharmacodynamic effects

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

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. In cell culture studies, the susceptibility of SARS-CoV-2 to inhibition by NHC did not substantially change as the NHC IC_{50} values showed <2-fold change over the 30 passages.

Clinical efficacy and safety

Clinical data are based on data from 1433 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT was 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 Lagevrio 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. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia.
Forty-eight percent of subjects received Lagevrio 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%). Among 792 subjects (55% of total randomised population) with available 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. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 2 provides the results of the primary endpoint (the percentage of subjects who were hospitalised or died through Day 29 due to any cause).

Table 2: Efficacy Results in Non-Hospitalised Adults with COVID-19

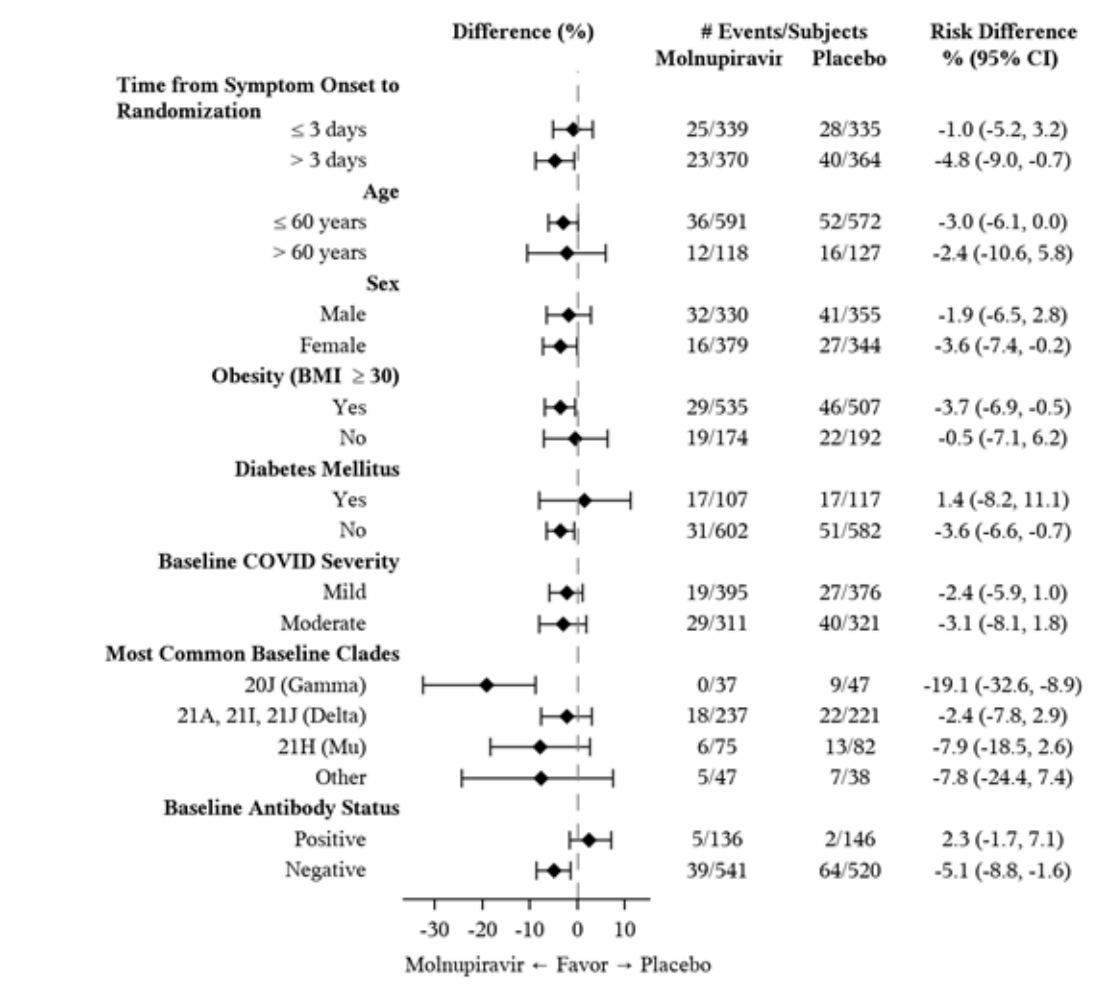
Interim Analysis				
	Lagevrio (N=385) n (%)	**Placebo (N=377) n (%)**	**Risk difference* (95% CI)**	**p-value†**
All-cause hospitalisation or death through Day 29[†]	28 (7.3%)	53 (14.1%)	-6.8% (-11.3%, -2.4%)	0.0012
Hospitalisation	28 (7.3%)	52 (13.8%)		
Death	0 (0%)	8 (2.1%)		
Unknown[‡]	0 (0%)	1 (0.3%)		
All-Randomised Analysis				
	Lagevrio (N=709) n (%)	**Placebo (N=699) n (%)**	**Risk difference* (95% CI)**	
All-cause hospitalisation or death through Day 29	48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)	
Hospitalisation[‡]	48 (6.8%)	67 (9.6%)		
Death	1 (0.1%)	9 (1.3%)		
Unknown[§]	0 (0%)	1 (0.1%)		

* Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
[†] 1-sided p-Value
[‡] Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
[§] Subjects with unknown status at Day 29 are counted as having an outcome of all-cause hospitalisation or death in the efficacy analysis.
Note: All subjects who died through Day 29 were hospitalised prior to death.

For interim analysis subjects: Relative risk reduction of molnupiravir compared to placebo is 48% (95% CI: 20%, 67%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
For all randomised subjects: Relative risk reduction of molnupiravir compared to placebo is 30% (95% CI: 1%, 51%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Efficacy results were consistent across the majority of sub-groups (Figure 1).

Figure 1. Subgroup Efficacy Results in Non-Hospitalised Adults with COVID-19 - All-Randomised Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

Paediatric population
The Agency has deferred the obligation to submit the results of studies with Lagevrio in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

Viral RNA Rebound
Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

Exceptional circumstances
This medicine has been authorised under 'exceptional circumstances'.
This means that it has not been possible to obtain complete information on this medicine.
The Medicines and Healthcare product Regulatory Agency (MHRA) will review any new information which may become available every year and this SmPC will be updated as necessary.

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.

The pharmacokinetics of NHC in patients with COVID-19 at steady-state following administration of 800 mg molnupiravir every 12 hours are provided below in Table 3.

Table 3: Pharmacokinetics of NHC in Patients with COVID-19 after administration of 800mg Lagevrio every 12 hours*

NHC Geometric Mean (%CV)		
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	**C_{max} (ng/mL) †**	**C_{12hr} (ng/mL)**
8810 (41.2)	2600 (31.7)	30.9 (115)
%CV: Geometric coefficient of variation *Values were obtained from population PK analysis. †The C_{max} estimate from a Phase 1 study of healthy subjects was 2970 ng/mL (16.8%)		

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}), but AUC was not significantly affected.
Molnupiravir can be taken with or without food.

Distribution
NHC does not bind to plasma proteins.

Metabolism
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

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 Patients
Lagevrio 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 clinical study, no significant difference in the PK of NHC was observed in subjects with severe renal impairment (eGFR less than 30 mL/min/1.73m^2) compared to healthy subjects. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics of NHC. The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients on dialysis (see section 4.2).

Hepatic Impairment
Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination. In a clinical study, no significant difference in the PK of NHC was observed in subjects with moderate hepatic impairment (Child-Pugh class B) compared to healthy subjects. No dose adjustment in patients with hepatic impairment is needed (see section 4.2).

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 (less than the human NHC exposure at the recommended human dose (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 (21 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (10 and 17 times the human NHC exposure at the RHD in female and male rates, 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 (6 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 (5 and 9 times the human NHC exposure at the RHD in female and male rats, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (2 times the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (21 times the human NHC exposure at the RHD). In juvenile rat studies, adverse findings were limited to decreased bone formation in the patella observed

when juvenile rats were exposed to NHC AUC exposures 7-fold (postnatal day 50) to 27-fold (postnatal day 10) the clinical NHC exposure. These bone and cartilage findings are not relevant for adult humans with mature skeletal development. The clinical significance of these findings for paediatric patients is unknown.

Carcinogenesis

Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

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 assays in somatic and germ cells) 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.

Impairment of Fertility

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 7 times, respectively, the human NHC exposure at the recommended human dose (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 (≥3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than 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 (20 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 ≥400 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (2 times the human NHC exposure at the RHD) from gestation day (GD) 6 through lactation day 20. No effects were observed in offspring. When molnupiravir was administered to lactating rats at ≥250 mg/kg/day, NHC was detected in plasma of nursing pups.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Croscarmellose sodium (E468)
Hydroxypropyl cellulose (E463)
Magnesium stearate (E470b)
Microcrystalline cellulose (E460)

Capsule shell:
Hypromellose (E464)
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink:
Butyl alcohol
Dehydrated alcohol
Isopropyl alcohol
Potassium hydroxide
Propylene glycol (E1520)
Purified water
Shellac
Strong ammonia solution
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store in the original package.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with a polypropylene closure containing 40 capsules.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53095/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/09/2025

10 DATE OF REVISION OF THE TEXT

24/09/2025