1 PRODUCT NAME

Lagevrio® (molnupiravir) 200 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lagevrio capsules contain the active substance molnupiravir for oral administration.

Each capsule contains 200 mg of molnupiravir.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lagevrio is available as a Swedish Orange opaque capsule with corporate logo and “82” printed with white ink. Each capsule is approximately 21.7 mm in length.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lagevrio has provisional consent [see section 5.1] for the indication below:

Lagevrio is indicated for the treatment of mild to moderate coronavirus disease (COVID-19) in adults aged 18 years and older who are at increased risk of progressing to severe COVID-19, hospitalisation or death.

4.2 Dose and method of administration

Adults

The recommended dose of Lagevrio in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.

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

Lagevrio 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].

Missed dose

If the patient misses a dose of Lagevrio 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.

Paediatric population

Safety and efficacy of Lagevrio have not been established in patients less than 18 years of age [see sections 4.4, 5.2 and 5.3].

Elderly patients

No dose adjustment of Lagevrio is recommended for geriatric patients [see section 5.2].

Renal impairment

No dose adjustment of Lagevrio is required in patients with renal impairment [see section 5.2].

Hepatic impairment

No dose adjustment of Lagevrio is recommended in patients with hepatic impairment [see section 5.2].

Pregnancy

Based on animal data, Lagevrio may cause fetal harm. Human pregnancy data are not available. The use of Lagevrio is not recommended during pregnancy [see sections 4.6 and 5.3]

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

Paediatric population

Safety and efficacy of Lagevrio have not been established in patients less than 18 years of age [see sections 4.2, 5.2 and 5.3].

Hypersensitivity

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

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 Lagevrio with concomitant medications have not been conducted. Molnupiravir is hydrolyzed to N4-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 drug metabolizing enzymes or transporters. Neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolizing enzymes or 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 Lagevrio (molnupiravir). It is also recommended that men who are sexually active with a partner of childbearing potential use an adequate form of contraception during and 3 months after treatment with Lagevrio.

Pregnancy

Consider the need for a pregnancy test before initiating treatment in women of childbearing potential who are sexually active.

Risk Summary

The use of Lagevrio is not recommended during pregnancy. Based on animal data, Lagevrio may cause fetal harm when administered to pregnant women. There are no available data on the use of Lagevrio in pregnant women to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended human dose (RHD) and reduced fetal 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 fetal body weights at 18 times the human NHC exposure at the RHD. In a pre- and post-natal developmental study in female rats, no effects were observed in offspring at exposures 2 times the human NHC exposure at the RHD [see section 5.3].

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, breastfeeding 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).

4.7 Effects on ability to drive and use machines

Lagevrio is predicted to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials Experience

The safety of Lagevrio was evaluated based on data from a Phase 3 double-blind trial (MOVe-OUT) in which 1411 non-hospitalised subjects with COVID-19 were randomised and treated with Lagevrio (N=710) or placebo (N=701) for up to 5 days and followed through Day 29. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation [see section 5.1].

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving molnupiravir and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; none was considered drug-related by the investigator and most were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) of the subjects receiving molnupiravir and 12 (1.7%) of subjects receiving placebo.

The most common adverse reactions in the molnupiravir treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving Lagevrio in MOVe-OUT*

	Lagevrio % **N=710**	**Placebo %** **N=701**
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities

Selected laboratory abnormalities reported through Day 29 are presented in Table 2.

Table 2: Selected Laboratory Abnormalities in MOVe-OUT

Criterion*	**Lagevrio** **N = 710**	**Placebo** **N = 701**
Chemistry		
Alanine Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	2%
Grade 4: ≥10.0 x ULN	<1%	0%
Aspartate Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	<1%
Grade 4: ≥10.0 x ULN	0%	0%
Creatinine (mg/dL)		
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	2%	2%
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	<1%	1%
Lipase (IU/L)		
Grade 3: 3.0-<5.0 x ULN	<1%	<1%
Grade 4: ≥5.0 x ULN	0%	1%
Hematology		
Hemoglobin (g/dL)		
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	<1%	1%
Grade 4: Male: <7.0 Female: <6.5	0%	0%
Platelets (10^9/L)		
Grade 3: 25 - <50	0%	0%
Grade 4: <25	0%	<1%
Leukocytes (10^9/L)		
Grade 3: 1.000 – 1.499	<1%	<1%
Grade 4: <1.000	0%	0%

*For graded criteria: subjects are counted once per test in the highest grade reported.

For inclusion in this analysis, both a baseline and at least one post-baseline laboratory value had to be present. Only subjects with a worsened grade from baseline were included.

Grades are based on the NIH DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 or predefined limit of change (PDLC).

Post-marketing Experience

The following adverse reactions have been identified during post-marketing use of Lagevrio. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders
vomiting

Immune System Disorders
hypersensitivity[see section 4.4]

Skin and Subcutaneous Tissue Disorders
angioedema, erythema, pruritus, 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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.

Therapeutic class

Lagevrio is an antiviral drug.

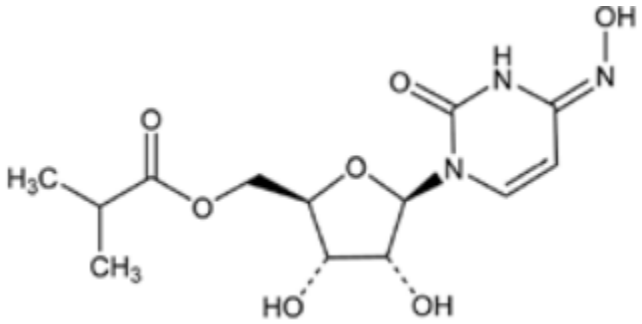
Chemistry

Molnupiravir is the 5´-isobutyrate prodrug of the antiviral ribonucleoside analogue NHC.

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl}oxolan-2-yl]methyl 2-methylpropanoate.

It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol.

Its structural formula is:



Molnupiravir is a white to off-white solid that is soluble in water.

Mechanism of action

Lagevrio is a prodrug that is metabolized to the cytidine nucleoside analogue, 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.

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

Clinical Trials

Clinical data are based on data from 1433 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT 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 are 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: over 60 years of age, 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 randomisation. 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); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian; 50% 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 molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (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 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalised or died through Day 29 due to any cause).

Table 3. 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%)		

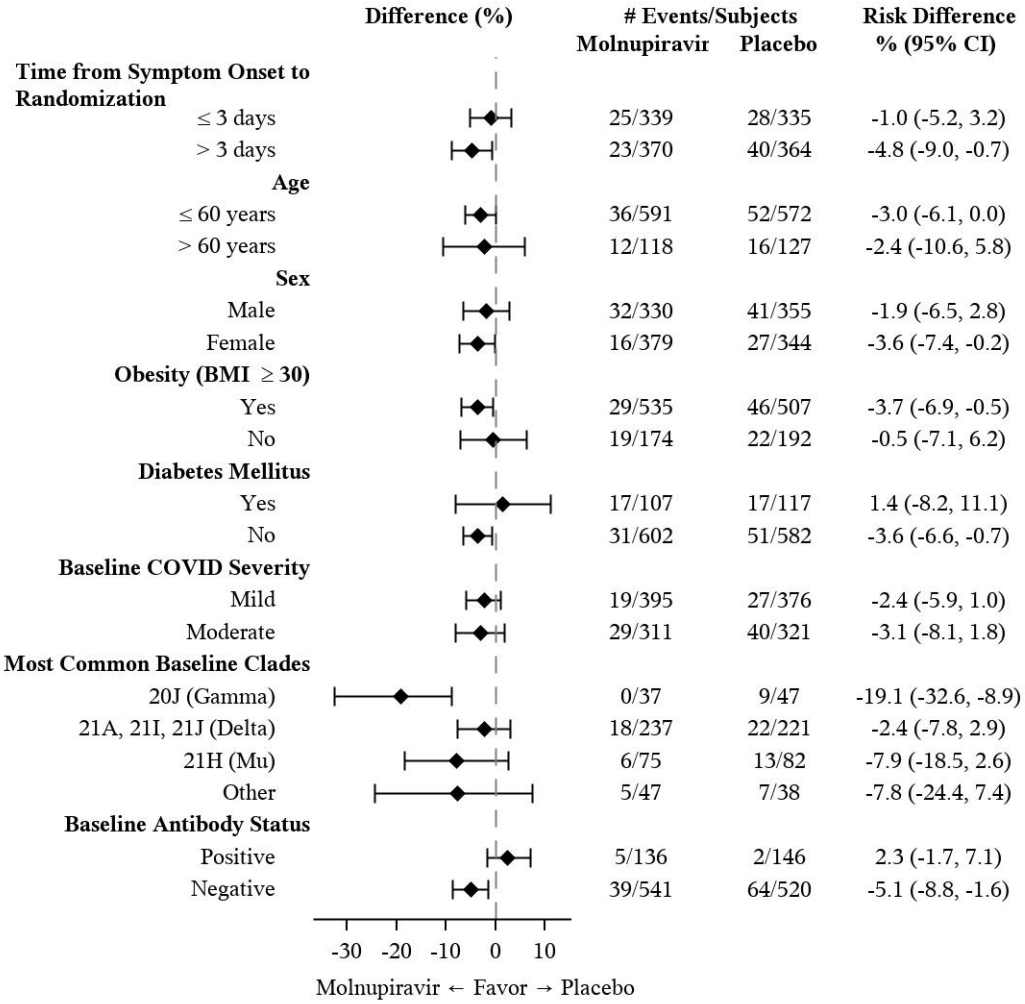
* Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
† 1-sided p-Value
‡ Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
§ Subjects with unknown status 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)

An exploratory analysis assessing the primary endpoint in prespecified subgroups is provided in Figure 1. For the majority of subgroups, the point estimate favours molnupiravir.

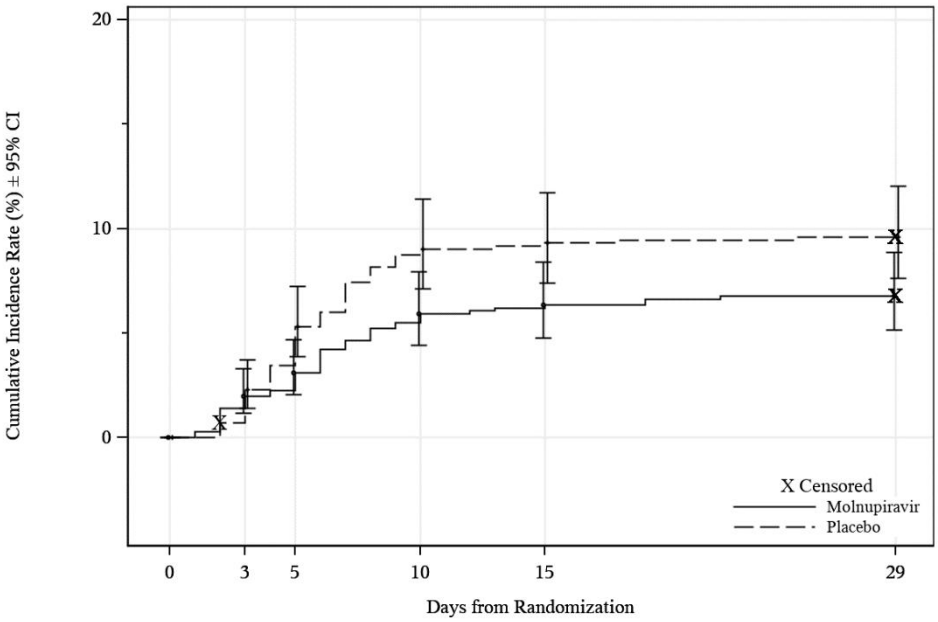
Figure 1. Subgroup Efficacy Results in Non-Hospitalised Adults with COVID-19 - All-Randomised Subjects



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.

The Kaplan-Meier curve shows time to hospitalisation or death, and results are consistent with the primary results (Figure 2).

Figure 2. Kaplan-Meier Plot of Time to Hospitalisation or Death Through Day 29 – All-Randomised Subjects



Number of participants at risk

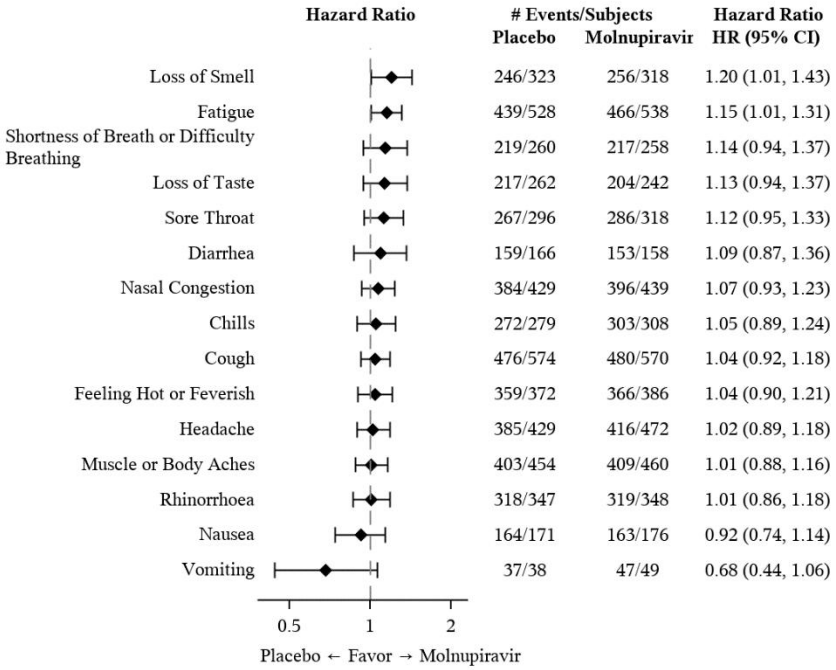
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631

Number of events inside period

Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

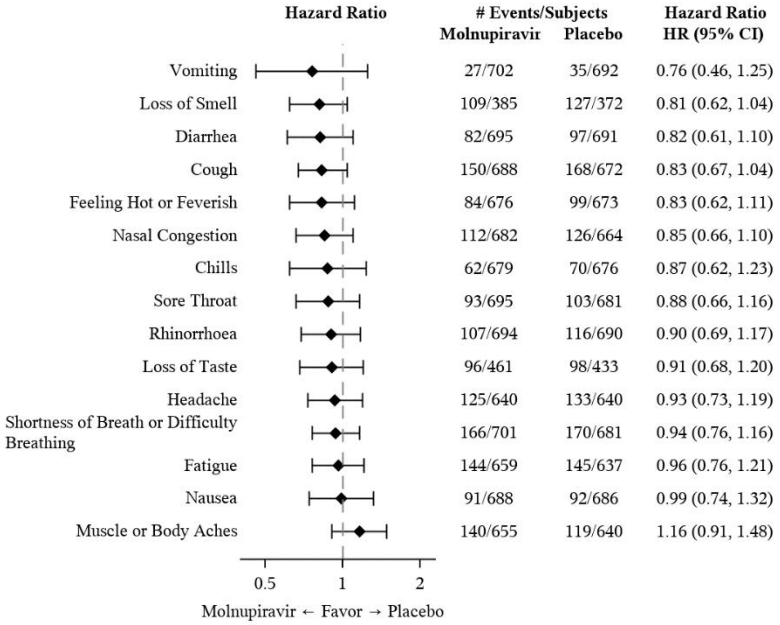
Higher percentages of subjects reported sustained improvement or resolution in most self-reported COVID-19 signs and symptoms, as recorded on a daily symptom diary, in the molnupiravir group compared to the placebo group (Figure 3). Lower percentages of subjects reported progression in most self-reported COVID-19 signs and symptoms, as recorded on a daily symptom diary, in the molnupiravir group compared to the placebo group (Figure 4).

Figure 3. Hazard Ratio of Time to Sustained Improvement or Resolution of Signs and Symptoms Through Day 29 – All-Randomised Subjects



Based on Cox regression model with Efron's method of tie handling with treatment and randomisation stratification factor as covariates. Hazard ratio > 1 favours the molnupiravir group.

Figure 4. Hazard Ratio of Time to Progression of Signs and Symptoms Through Day 29 – All-Randomised Subjects



Based on Cox regression model with Efron's method of tie handling with treatment and randomisation stratification factor as covariates. Hazard ratio < 1 favours the molnupiravir group.

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.1.351 (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 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 SARS-CoV-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 hydrolyzed 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 4.

Table 4: Pharmacokinetics of NHC 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)***
8260 (41.0)	2970 (16.8)	31.1 (124)
%CV: Geometric coefficient of variation * Values were obtained from population 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 (Tmax) was 1.5 hours.

Effect of Food

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 metabolizing enzymes or transporters. Neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolizing 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.

Special populations

Paediatric population

The pharmacokinetics of molnupiravir in paediatric patients less than 18 years of age have not been evaluated [see sections 4.2, 4.4 and 5.3].

Gender, race and age

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

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 PK of NHC. While the PK 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 PK of molnupiravir and NHC has not been evaluated in patients with hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure. 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 hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than 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 hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in female and male rats, 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 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 and 7 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 2000 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.

Carcinogenicity

Carcinogenicity studies with molnupiravir have not been conducted.

Mutagenicity

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 embryofetal 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 1000 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 1000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal 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 1000 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 fetal 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.

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

Each Lagevrio capsule contains the following inactive ingredients:
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Microcrystalline cellulose
Purified water

The capsule shell contains:
Hypromellose
Red iron oxide
Titanium dioxide

The white ink contains:
Butyl alcohol
Dehydrated alcohol
Isopropyl alcohol
Potassium hydroxide
Propylene glycol
Purified water
Shellac
Strong ammonia solution
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store Lagevrio in the original bottle.

Store Lagevrio below 30°C.

6.5 Nature and contents of container

HDPE bottle containing 40 capsules.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Restricted medicine (pharmacist-only medicine).

8 SPONSOR

Merck Sharp & Dohme (New Zealand) Limited
PO Box 99851
Newmarket
Auckland 1023
New Zealand
Tel: 0800 500 673

9 DATE OF FIRST APPROVAL

14 April 2022

10 DATE OF REVISION OF THE TEXT

13 September 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of ‘vomiting’ and ‘pruritus’

RCN: 000026043