ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES

FOR

UNAUTHORISED PRODUCT
Lagevrio (molnupiravir)

AVAILABLE FOR USE

1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for use: Lagevrio**
- **Active substance(s): molnupiravir**
- **Pharmaceutical form: Capsule**
- **Route of administration: Oral Use**
- **Strength: 200 mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

[Contact details will be added at the National level]

3. TARGET POPULATION

Lagevrio is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. See section 6.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

5.1 Posology

- **Dosing recommendations and treatment duration**

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

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

- **Specific populations**

Paediatric population
The safety and efficacy of Lagevrio in patients below 18 years of age have not yet been established. No data are available.

Elderly
No dose adjustment of Lagevrio is required.

Renal impairment
No dose adjustment of Lagevrio is required. See section 5.3.

Hepatic impairment
No dose adjustment of Lagevrio is required. See section 5.3.

- **Method of administration**

For oral use.
Lagevrio 200 mg capsules can be taken with or without food.

Patients should be advised to swallow the capsules whole and not to open, break, or crush the capsule.

5.2 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 5.11).

5.3 Special warnings and precautions for use

Renal and hepatic impairment

Patients with severe renal impairment were excluded from clinical trials. There is limited experience of the use of molnupiravir in persons with any degree of hepatic impairment.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially 'sodium-free'.

5.4 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed with molnupiravir. No substantial risks for clinically important drug interactions when dosing with molnupiravir 800 mg every 12 hours for 5 days have been identified based on the limited available in-vitro data.

5.5 Pregnancy and lactation

- **Women of childbearing potential**

Women of childbearing potential must use effective contraception for the duration of treatment and for 4 days after the last dose of Lagevrio.

- **Pregnancy**

There are no data from the use of Lagevrio in pregnant women. Studies in animals have shown reproductive toxicity. Oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 7.5 times the human NHC exposures at the recommended human dose (RHD) and reduced foetal growth at ≥ 2.9 times the human N-hydroxycytidine (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. The safety margin at the NOAEL to human NHC exposure is 0.8 times and 6.5 times at the RHD in rats and rabbits, respectively. Although maternal toxicity was observed in both rats and rabbits at all dose levels in which developmental toxicity occurred, a substance-related effect cannot be excluded.

Lagevrio is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

- **Breast-feeding**

It is unknown whether Lagevrio or any of the components of Lagevrio are present in human milk, affect human milk production, or have effects on the breastfed infant. Animal lactation studies with molnupiravir have not been conducted.

Based on the potential for adverse reactions on the breastfeeding infant from Lagevrio, breast-feeding should be interrupted during treatment and for 4 days after the last dose of Lagevrio.

- **Fertility**

No human data on the effect of molnupiravir on fertility are available. There were no effects on female or male fertility in rats at approximately 2 and 6 times the human NHC exposure at the RHD respectively.

5.6 Incompatibilities

Not applicable.

5.7 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.

5.8 Shelf life

18 months

5.9 Storage conditions

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

5.10 Special precautions for disposal

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

5.11 List of excipients

Capsule content:
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Microcrystalline cellulose
Purified water

Capsule shell:
Hypromellose
Titanium dioxide
Red iron oxide

Printing ink:
Potassium hydroxide
Shellac
Titanium dioxide

6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile

The most common adverse reactions reported during treatment with 800 mg every 12 hours for 5 days and during 14 days after the last dose were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

Tabulated list of adverse reactions
The adverse reactions 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**
Nervous sytem disorders	
Common	dizziness, headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
Uncommon	vomiting
Skin and subcutaneous tissue disorders	
Uncommon	rash, urticaria

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 national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action
Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue N - hydroxycytidine (NHC). NHC distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). 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. This mechanism of action is referred to as 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 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.

Resistance

Studies to evaluate resistance to NHC with SARS-CoV-2 in cell culture and in clinical studies have not been completed. In-vitro resistance selection studies with other coronaviruses (Murine Hepatitis Virus and MERS-CoV) 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 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.

- **Summary of relevant Clinical properties**

Clinical efficacy and safety

Clinical data are based on an interim analysis of data from 775 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT was a randomised, double blind and placebo-controlled trial in non-hospitalised adult patients with laboratory-confirmed COVID-19.

Eligible patients had not been vaccinated against SARS-CoV-2 and had symptom onset within 5 days of enrolment. At study entry, patients were not receiving supplemental oxygen and had at least one of the protocol-listed risk factors for progression to severe COVID-19 (60 years of age or older, diabetes, obesity [BMI >30], chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease or active cancer). Subjects were randomised 1:1 to receive 800 mg of Lagevrio or placebo orally every 12 hours for 5 days.

At baseline the median age was 44 years (range: 18 to 88 years); 14% of patients were 60 years of age or older and 3% were over 75 years of age; 52% were male; 52% were White, 6% Black or African American and 2% Asian; 58% were Hispanic or Latino. Forty-nine percent of subjects received Lagevrio or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (77%), 60 years of age or older (14%) and diabetes (14%). 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: Interim Efficacy Results in Non-Hospitalised Adults with COVID-19

	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%)		

* 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). Relative risk reduction of molnupiravir compared to placebo is 52% (95% CI: 33%, 80%) based on the Cochran-Mantel-Haenszel 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 hospitalization or death in the efficacy analysis.
Note: All subjects who died through Day 29 were hospitalised prior to death.

Efficacy results were consistent across sub-groups including age (>60 years), at risk medical conditions (e.g., obesity, diabetes) and SARS-CoV-2 variants. In the subgroup of subjects positive for SARS-CoV-2 antibodies at baseline (approximately 18%; reflecting current or prior infection), there was no difference for the primary endpoint between the molnupiravir and placebo groups.

7. CONDITIONS FOR SAFETY MONITORING

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.