This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[CV021 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited, Goa (Unit-VII) Plot No. S- 103 to S- 105, S-107 to S-112 & L-147, L-147/1 to L-147/3, L-147/A & L-138, Verna Industrial Estate, Verna, Salcette, Goa – 403 722, India
Active Pharmaceutical Ingredient (API)	Molnupiravir
Pharmaco-therapeutic group (ATC Code)	J05AB18
Therapeutic indication	[CV021 trade name] is indicated for treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe.

1. Introduction

[CV021 trade name] is indicated for treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe.

The management of COVID-19 should follow the most recent authoritative guidelines, including those issued by WHO.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

Data provided in the dossier show that molnupiravir, [(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hyroxyamino)-2-oxopyrimidin-1-yl] oxolan-2-yl] methyl-2-methylpropanoate, is a white to an off-white crystalline powder and it is freely soluble in methanol. Solubility data provided indicate that the API is highly soluble according to the BCS.

The manufacturer consistently produces an anhydrous crystalline form, which is characterized by x-ray powder diffraction.

The API specifications include tests for description, solubility, identification (IR and HPLC), water content (KF), residue on ignition, specific optical rotation, related compounds (HPLC), assay (HPLC), residual solvents (GC), bulk density and polymorphic form (p-XRD).

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the capsule fill formulation include microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate. The capsule shell contains hypromellose, titanium dioxide, yellow iron oxide and black iron oxide. None of the excipients used in the manufacture of the capsules are of human or animal origin. A TSE/BSE free certificate has been provided for magnesium stearate. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[CV021 trade name] is a hard cellulose capsule with an opaque dark green cap and body. It contains a white to off-white granular powder.

The capsules are packaged in opaque white plastic (HDPE) bottles. Each bottle has a cardboard /aluminium foil heat seal liner and a white plastic (HDPE) childproof plastic screw cap.

The development of the proposed product was initiated with the review of the technical package from Merck Sharp & Dohme. The objective was to develop an immediate release solid oral dosage form with similar manufacturing formula and manufacturing process that is bioequivalent to the WHO recommended comparator product, Lagevrio® (molnupiravir) 200 mg capsules. Based on literature information, physicochemical characteristics of the API and the API-excipient compatibility study, a wet granulation process was selected for the manufacture of the granules. The rationale for selection of the wet granulation process was to obtain granules with adequate flow properties. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and HPLC-PDA detection), water content (KF), uniformity of dosage units (by mass variation), assay (HPLC), dissolution (HPLC detection), related substances (HPLC), residual solvents and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are regarded acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

A randomized, single dose, open label, two-treatment, two-period, cross-over oral bioequivalence study between the test product, Molnupiravir 200 mg capsule (Cipla Ltd., India) and the reference product, Lagevrio (molnupiravir) 200 mg capsule (marketed by: Merck Sharp & Dohme (UK)

Limited, 120 Moorgate, London, EC2M 6UR, United Kingdom), in healthy adult human subjects under fasting conditions (study no. 21-11-264).

The objective of the study was to compare the bioavailability of the stated Molnupiravir 200 mg capsule manufactured by/for Cipla Ltd., India (test drug) with the reference formulation Lagevrio® (MSD) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 capsule Molnupiravir 200 mg (molnupiravir 200 mg) Batch no. GG20137.

Treatment R: Reference – 1 capsule Lagevrio® 200 mg (molnupiravir 200 mg) Batch no. U038659.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 16h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for the active metabolite N-hydroxycytidine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for N-hydroxycytidine.

The study was performed with 60 participants; data generated from a total of 59 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for N-hydroxycytidine as well as statistical results are summarised in the following table:

N-hydroxycytidine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.40 ± 0.51	1.34 ± 0.54	–	–
C_{max} (ng/mL)	1287 ± 321 (1247)	1305 ± 359 (1257)	99.2	93.4 – 105.4
AUC_{0-t} (ng·h/mL)	2668 ± 590 (2603)	2686 ± 675 (2599)	100.2	96.9 – 103.5
AUC_{0-inf} (ng·h/mL)	2694 ± 589 --	2710 ± 677 --	–	–

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding N-hydroxycytidine. Accordingly, the test Molnupiravir 200 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Lagevrio® (MSD).

4. Summary of product safety and efficacy

[CV021 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [CV021 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Lagevrio® (MSD) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [CV021 trade name] is considered acceptable when

guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [CV021 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV021 trade name] has been shown to be bioequivalent with Lagevrio® (MSD).

Efficacy and Safety

Regarding clinical efficacy and safety, [CV021 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [CV021 trade name] was acceptable for the following indication: 'for treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe ', and would allow inclusion of [CV021 trade name], manufactured at Cipla Limited, Goa (Unit-VII),Plot No. S- 103 to S- 105, S-107 to S-112 , & L-147, L-147/1 to L-147/3, L-147/A & L-138, Verna Industrial Estate, Verna, Salcette, Goa – 403 722, India in the list of prequalified medicinal products.