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	[CV022 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited, F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik - 422 113 Maharashtra India.
Active Pharmaceutical Ingredient(s) (API)	Molnupiravir
Pharmaco-therapeutic group (ATC Code)	Nucleosides and nucleotides excluding reverse transcriptase inhibitors (J05AB18)
Therapeutic indication	[CV022 trade name] is indicated for treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe.

1. Introduction

[CV022 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 is a white to an off-white crystalline powder. Solubility data provided indicate that the API is highly soluble according to the BCS.

The manufacturer consistently produces an anhydrous crystalline form.

The API specifications include tests for description, solubility, identification (IR and HPLC), water content (KF), residue on ignition, specific optical rotation, related substances (HPLC), assay (HPLC), residual solvents (GC-HS and GC-MS) and identification of polymorph (p-XRD).

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.

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

Other ingredients

Other ingredients used in the capsule fill formulation include hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate all being pharmacopoeial controlled. The capsule shell contains titanium dioxide and hypromellose, while the printing ink contains shellac, black iron oxide and potassium hydroxide, all being controlled by acceptable specifications. None of the excipients are of animal or human origin. TSE/BSE free certificates from the suppliers have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[CV022 trade name] is a hard hypromellose capsule with an opaque white cap and body. It is printed in black on the cap with 'M200' and on the body with 'V'. It contains a white to off white granular powder.

The capsules are packaged in a round, opaque white plastic (HDPE) bottle. The bottle has an aluminium/plastic foil seal and an opaque white plastic (polypropylene) 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 that is bioequivalent to the WHO recommended comparator product, Lagevrio® (molnupiravir) 200 mg capsules. The quality target product profile was defined based on the properties of the API and characterization of the comparator product; the critical quality attributes were also identified. The excipients used in [CV022 trade name] were selected based on the excipients used in the comparator product, API-excipient compatibility studies and their functionality for development of the capsule dosage form. Since the API exhibits very poor flow characteristics, a wet granulation manufacturing process was selected to facilitate the distribution of the API throughout the blend and to improve the blend flow. 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 IR), dissolution (by HPLC detection), uniformity of dosage units (by weight variation), related substances (HPLC), water content (KF), assay (HPLC), average fill weight of capsule, colour identification (for titanium dioxide) 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.

Single-dose, fasting bioequivalence study of Mylan's test product Molnupiravir capsules 200 mg manufactured by Mylan Laboratories Ltd., India with Reference product Lagevrio 200 mg hard capsules of Merck Sharp & Dohme (UK) Limited, in healthy adult human subjects (study no. MOLN-CAZ-1001).

The objective of the study was to compare the bioavailability of the stated Molnupiravir 200 mg capsule manufactured by/for Mylan Laboratories 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. 2023232.

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 16 h 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/ml for N-hydroxycytidine.

The study was performed with 39 participants; data generated from a total of 37 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)	1.25 (0.75 – 3.00)	1.00 (0.50 – 3.00)	–	–
C_{max} (ng/mL)	1152 ± 310 (1110)	1119 ± 358 (1060)	104.7	98.0 – 111.9
AUC_{0-t} (ng·h/mL)	2241 ± 458 (2193)	2152 ± 498 (2094)	104.7	100.2 – 109.5
AUC_{0-inf} (ng·h/mL)	2254 ± 456	2165 ± 498		

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

[CV022 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, [CV022 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 [CV022 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 [CV022 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV022 trade name] has been shown to be bioequivalent with Lagevrio® (MSD).

Efficacy and Safety

Regarding clinical efficacy and safety, [CV022 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 [CV022 trade name] was acceptable for the following indication: ' treating non-severe COVID-19 in adults who are at high risk of their disease becoming severe.', and would allow inclusion of [CV022 trade name], manufactured at Mylan Laboratories Limited, F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik - 422 113, Maharashtra, India in the list of prequalified medicinal products.