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	[CV008 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit-V Survey No. 439, 440, 441 & 458, TSIIC-Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar District Telangana State, 509 301 India
Active Pharmaceutical Ingredient(s) (API)	Molnupiravir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, direct acting antivirals (ATC code: not yet assigned)
Therapeutic indication	Treatment of mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe.

1. Introduction

[CV008 trade name] is indicated for treating mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe.

Treatment with [CV008 trade name] should be started as soon as possible after diagnosing COVID-19 and within 5 days of the onset of COVID-19 symptoms.

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 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.

Molnupiravir exhibits polymorphism. The manufacturer consistently produces anhydrous crystalline form I, which is characterized by X-ray powder diffraction (XRPD).

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

The API specifications include tests for description, solubility, identification (IR and HPLC), polymorphic form (XRPD), water content (KF), residue on ignition, specific optical rotation, related compounds (HPLC), assay (HPLC), residual solvents (GC) and particle size (laser diffraction).

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 gelatin, iron oxide yellow, titanium dioxide, FD&C blue #2/indigo carmine, hypromellose, carrageenan and potassium acetate while the printing ink contains shellac, propylene glycol, potassium hydroxide and titanium dioxide. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[CV008 trade name] capsules are white to off-white granular powder filled in size '0' hard cellulose capsules with green opaque cap imprinted with "H" in white colour and green opaque body imprinted with "M11" in white colour. The capsules are packaged in HDPE bottles and cold form Alu-Alu blister cards.

The development of the final composition of the capsules has been described. The objective was to develop an immediate release solid oral dosage form, bioequivalent to the WHO recommended comparator product, Lagevrio® (molnupiravir) 200mg capsules (Merck Sharp & Dohme). With reference to the technical package from MSD, the comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility data. The manufacturing process which was selected for the finished pharmaceutical product involved high shear wet granulation, wet de-agglomeration, fluid bed drying, dry milling, blending, lubrication and encapsulation. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics. 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 detector), average net fill content, average weight of filled capsules, lock length, water content (KF), uniformity of dosage units (by weight variation), assay (HPLC), dissolution (HPLC detection), related substances (HPLC) 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 conditions in the packaging proposed for marketing of the product. The data indicated that no out-of-specification or significant change was observed and all parameters were well within the agreed limits at both 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.

An open-label, balanced, randomized, single oral dose, two-treatment, two-sequence, two-period, cross over, bioequivalence study comparing Molnupiravir capsules 200 mg of Hetero Labs Limited, India ([CV008 trade name]), with Lagevrio® (molnupiravir) capsules 200 mg of Merck Sharp & Dohme in normal healthy, adult, human, subjects under fasting conditions (study no. 133-21).

The objective of the study was to compare the bioavailability of the stated Molnupiravir 200 mg capsule manufactured by/for Hetero Labs. Limited, 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 [CV008 trade name]
(molnupiravir 200 mg)
Batch no. MOL22001.

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

A 8 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 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 42 participants; data generated from a total of 42 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)	1.54 ± 0.58	1.38 ± 0.52	–	–
C_{max} (ng/mL)	1510 ± 424 (1453)	1461 ± 359 (1417)	102.6	96.0 – 109.5
AUC_{0-t} (ng·h/mL)	3372 ± 766 (3283)	3340 ± 651 (3277)	100.2	96.6 – 104.0
AUC_{0-inf} (ng·h/mL)	3402 ± 765 –	3371 ± 652 –	–	–

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

[CV008 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, [CV008 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Lagevrio® (Merck Sharp & Dohme) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [CV008 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 [CV008 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV008 trade name] has been shown to be bioequivalent with Lagevrio® (Merck Sharp & Dohme).

Efficacy and Safety

Regarding clinical efficacy and safety, [CV008 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 [CV008 trade name] was acceptable for the following indication: 'treating mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe', and would allow inclusion of [CV008 trade name], manufactured at Hetero Labs Limited, Unit-V, Survey No. 439, 440, 441 & 458, TSIIC-Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar District, Telangana State, India, in the list of prequalified medicinal products.