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	[CV010 trade name]*
Manufacturer of Prequalified Product	Emcure Pharmaceuticals Limited Plot No. P-2, I.T.B.T. Park, Phase II, MIDC, Hinjwadi, Pune-411 057, Maharashtra, India Tel. No.: +91 20 39821300 Fax No.: +91 20 39821340
Active Pharmaceutical Ingredient (API)	Molnupiravir
Pharmaco-therapeutic group (ATC Code)	Nucleosides and nucleotides excl. reverse transcriptase inhibitors (J05AB18)
Therapeutic indication	Treatment of mild or moderate COVID-19 in adults at risk of their disease becoming severe.

1. Introduction

[CV010 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 [CV010 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 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 that is freely soluble in methanol. Solubility data indicate that the API is highly soluble according to the BCS.

The manufacturer consistently produces an anhydrous crystalline form, which is characterised 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) 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, carrageenan, potassium acetate and titanium dioxide, while the printing ink contains shellac, propylene glycol, black iron oxide and potassium hydroxide. None of the excipients used in the manufacture of the capsules are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[CV010 trade name] are white to off-white granular powder filled in a size '0' cellulose capsule consisting of white opaque cap imprinted with 'EM66' in black ink and white opaque body imprinted with 'EM66' in black ink. The capsules are packaged in HDPE bottles, closed with white opaque polypropylene, child resistant closures with heat seal liner.

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) 200 mg capsules (Merck Sharp & Dohme, MSD). With reference to the technical package from MSD, the comparator product was characterised and, on that basis, a quality target product profile was defined and critical quality attributes were identified.

Cellulose capsule shell composed of hypromellose was selected for encapsulation of the lubricated blend. It is widely used in oral dosage forms, generally considered non-irritant and non-toxic upon oral administration.

The excipients were selected based on those used in the comparator product and API-excipient compatibility data.

Based on literature information, characterisation of the active pharmaceutical ingredient 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 is to obtain granules with uniform distribution of the API, with improved flow properties to aid the capsule filling process.

Formulation trials optimised 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-diode array detection), assay (HPLC), dissolution (HPLC detection), water content (KF), uniformity of dosage units (by weight variation), 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 6 months at accelerated conditions in the packaging proposed for marketing of the product. No significant change was observed and all parameters were well within the agreed limits at both storage conditions, with only a slight increase of the total degradation products. 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, randomised, two-treatment, two-sequence, two-period, two-way crossover, single oral dose bioequivalence study of molnupiravir capsules 200 mg from Emcure Pharmaceuticals Ltd, India and Lagevrio® 200 mg hard capsules (molnupiravir capsule 200 mg) form Merck Sharp & Dohme (UK) Ltd, United Kingdom, in normal, healthy, adult, human subjects under fasting conditions (study no. BE/21/500).

The objective of the study was to compare the bioavailability of the stated molnupiravir 200 mg capsule form Emcure Pharmaceuticals Ltd (test drug) with the reference formulation Lagevrio® (MSD) and to assess bioequivalence. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T	Test – 1 capsule molnupiravir 200 mg (molnupiravir 200 mg) Batch no. H211040C
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 20 samples within 24 hours after the 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 20 ng/mL for N-hydroxycytidine.

The study was performed with 48 participants; data generated from a total of 45 subjects were used 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} (hours)	1.28 ± 0.46	1.19 ± 0.41	–	–
C_{max} (ng/mL)	1421 ± 399 (1367)	1372 ± 418 (1311)	104.2	96.3–112.8
AUC_{0-t} (ng·h/mL)	2819 ± 511 (2771)	2766 ± 628 (2699)	102.7	98.2–107.4
$AUC_{0-\infty}$ (ng·h/mL)	289 ± 512	2827 ± 630	–	–

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values for the active metabolite, 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

[CV010 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, [CV010 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 [CV010 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 [CV010 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV010 trade name] has been shown to be bioequivalent with Lagevrio® (MSD).

Efficacy and Safety

Regarding clinical efficacy and safety, [CV010 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 [CV010 trade name] was acceptable for the following indication: ‘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’, and would allow inclusion of [CV010 trade name] – manufactured at Emcure Pharmaceuticals Ltd, Pune, Maharashtra, 411 057, India – in the list of prequalified medicinal products.