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	[CV024 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited, FDF-I F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik - 422 113 Maharashtra, India.
Active Pharmaceutical Ingredient(s) (API)	Nirmatrelvir + ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors, ATC code: J05AE30
Therapeutic indication	[CV026 trade name] is indicated for treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19.

1. Introduction

[CV024 trade name] is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19.

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)

Nirmatrelvir

Nirmatrelvir has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [CV024 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Ritonavir

Bulk ritonavir 100mg film-coated tablets manufactured by Mylan Laboratories Limited (HA467, prequalified by WHO-PQ) is sourced for co-blistering. In this regard the application relies on HA467 for information on ritonavir API.

Other ingredients

Other ingredients used in the nirmatrelvir core tablet formulation include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains titanium dioxide, hypromellose, macrogol/PEG and iron oxide red. Lactose monohydrate is from bovine origin. TSE/BSE compliance declarations were provided for all the excipients.

Other ingredients used in the ritonavir core tablet formulation include sorbitan monolaurate, copovidone, colloidal silicon dioxide, sodium chloride and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains colloidal anhydrous silica, hypromellose, hydroxypropyl cellulose, iron oxide yellow, macrogol/PEG, polysorbate 80, talc and titanium dioxide. TSE/BSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-packaged product, consisting of four and two dosage units of nirmatrelvir 150mg film-coated tablets and ritonavir 100mg film-coated tablets, respectively, per aluminium-aluminium foil blister card.

The ritonavir 100mg film-coated tablet is identical to HA467, the product of Mylan Laboratories Limited, prequalified for the treatment of HIV. The only difference is with regard to the container closure system.

Pharmaceutical development and manufacture

Nirmatrelvir 150mg film-coated tablets

The multisource product is a pink, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a beveled edge. The tablet has ‘T5’ debossed (stamped into) on one side and is plain on the other side.

The aim of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the Nirmatrelvir 150mg film-coated tablets of the WHO recommended comparator product, Paxlovid™ (Nirmatrelvir 150mg film-coated tablets and Ritonavir 100mg film-coated tablets; co-pack by Pfizer Labs). The excipients of the core tablets were selected based on the excipients used in the comparator product and API-excipient compatibility data. Nirmatrelvir exhibits very poor flow properties. Based on the physicochemical properties of the API and literature on the comparator product, dry granulation (compaction process) was selected as the manufacturing process, thereby improving the flow properties and achieving uniform distribution of the API in the formulation. The manufacturing process was validated and dissolution profile similarity with the comparator tablets was also demonstrated. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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

Ritonavir100mg film-coated tablets

The multisource product is a yellow, capsule-shaped, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has ‘M 163’ debossed (stamped into) on one side and is plain on the other side.

Specifications

The specifications for nirmatrelvir 150mg film-coated tablets include tests for description, identification of API (IR, LC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (LC), water content (KF), related substances (UPLC) and microbial limits. The test procedures have been adequately validated.

The specifications for ritonavir 100mg film-coated tablets include tests for description, identification of the API (HPLC and TLC) and titanium dioxide (colour test), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), water content (KF), absence of crystalline ritonavir (p-XRD) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the co-blistered product. The data provided indicate that all the tested parameters remained within limits with no obvious trend or variability at both storage conditions.

The absence (below detection limit) of the crystalline form of the ritonavir API in the ritonavir film-coated tablets was demonstrated by p-XRD up to 6 months at accelerated storage condition and up to 18 months at long-term storage condition.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2023 according to internationally accepted guidelines.

Study title: Single-dose, fasting bioequivalence study of Nirmatrelvir 150 mg film-coated tablets plus Ritonavir 100 mg film-coated tablets (co-packaged for oral use) of Mylan Laboratories Limited, India with Paxlovid (nirmatrelvir 150 mg film-coated tablets; Ritonavir 100 mg film-coated tablets) of Pfizer (copackaged for oral use) in normal healthy adult human subjects (study no. NIRI-TFZ-1002).

The objective of the study was to compare the bioavailability of the stated Nirmatrelvir 150 mg tablet (co-packed with Ritonavir 100 mg tablets) manufactured for/by Mylan Laboratories Limited, India (test drug) with the reference formulation Paxlovid™ 150 mg (co-packed with Ritonavir 100 mg (Pfizer Labs)) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, fully replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments twice in a randomized fashion:

Treatment T:	Test – 2 tablets Nirmatrelvir 150 mg + 1 tablet Ritonavir 100 mg (nirmatrelvir 300 mg + ritonavir 100 mg) Batch no. 8146941
Treatment R:	Reference – 2 tablets Paxlovid™ 150 mg + 1 tablet Ritonavir 100 mg (nirmatrelvir 300 mg + ritonavir 100 mg) Batch no. GC4759

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36 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 nirmatrelvir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/ml for nirmatrelvir.

The study was performed with 54 participants; data generated from a total of 54 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for nirmatrelvir as well as statistical results are summarised in the following tables:

Nirmatrelvir

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)	2.25 ± 1.10	2.50 ± 1.23	–	–
C_{max} (ng/mL)	3466 ± 923 (3341)	3104 ± 784 (3009)	111.0	106.9 – 115.4
AUC_{0-t} (ng·h/mL)	33639 ± 9136 (32406)	31962 ± 7698 (31063)	104.3	101.0 – 107.8
AUC_{0-inf} (ng·h/mL)	34198 ± 9237 --	32489 ± 7815 --	–	–

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding nirmatrelvir. Accordingly, the test Nirmatrelvir 150 mg tablet (co-packed with Ritonavir 100 mg) meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Paxlovid™ (Pfzer Labs) (co-packed with Ritonavir 100 mg).

The Ritonavir 100 mg tablet has been prequalified under reference HA467.

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of ritonavir 100 mg tablets (Test) of Mylan Laboratories Limited, India and Norvir® (ritonavir) tablets 100 mg of AbbVie Inc, USA in healthy, adult, human subjects under fed conditions (study no. 186-16).

The objective of the study was to compare the bioavailability of the stated ritonavir 100 mg tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Norvir® 100 mg tablet (AbbVie Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Ritonavir 100 mg
(ritonavir 100 mg)
Batch no. 3053510

Treatment R: Reference – 1 tablet Norvir® 100 mg (ritonavir 100 mg) Batch no. 1056746

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 36 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for ritonavir.

The study was performed with 80 participants; data generated from a total of 70 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Ritonavir

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)	4.50 (2.00 – 7.00)	4.50 (2.00 – 6.00)	-	-
C_{max} (ng/mL)	859 ± 382 (787)	816 ± 316 (757)	104.0	97.3 – 111.0
AUC_{0-t} (ng·h/mL)	7067 ± 3406 (6438)	6824 ± 2925 (6248)	103.0	98.1 – 108.2
AUC_{0-inf} (ng·h/mL)	7367 ± 3614 --	7108 ± 3082 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ritonavir. Accordingly, the test ritonavir 100 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Norvir® 100 mg tablet (AbbVie Inc.).

4. Summary of product safety and efficacy

[CV024 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, [CV024 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Paxlovid™ 150 mg (co-packed with Ritonavir 100 mg (Pfizer Labs) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [CV024 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 [CV024 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV024 trade name] has been shown to be bioequivalent with Paxlovid™ 150 mg (co-packed with Ritonavir 100 mg (Pfizer Labs).

Efficacy and Safety

Regarding clinical efficacy and safety, [CV024 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 [CV024 trade name] was acceptable for the following indication: 'treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19', and would allow inclusion of [CV024 trade name], manufactured at Mylan Laboratories Limited, Sinnar, Nashik - 422 113, Maharashtra, India in the list of prequalified medicinal products.