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	[CV012 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit III Plot No. 22-110, IDA Jeedimetla, Hyderabad Telangana, 500 055 India
Active Pharmaceutical Ingredient(s) (API)	Nirmatrelvir, ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors, ATC code: J05AE30
Therapeutic indication	[CV012 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

[CV012 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.
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

Data provided in the dossier show that nirmatrelvir, (1R,2S,5S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, is a white to an off-white powder and it is freely soluble in methanol. Solubility data provided indicate that the API is critically insoluble in aqueous medium according to the BCS.

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

Nirmatrelvir exhibits polymorphism. The manufacturer consistently produces polymorphic form I, which is characterized by X-ray powder diffraction.

The API specifications include tests for description, solubility, identification (IR and HPLC), polymorphic form (p-XRD). water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), residual solvents (GC) and particle size distribution.

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.

Ritonavir

Ritonavir is described in the Ph.Int, Ph.Eur and USP. The API has four chiral centres, is practically insoluble in water and is known to exhibit polymorphism, with various crystal forms. The manufacture of ritonavir entails several steps and stereo selectively produces the desired stereoisomer. Polymorphic form I, characterised by X-ray powder diffraction, is consistently produced.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), polymorphic form (p-XRD), water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limits and genotoxic impurities (UFLC-MS; ≤ 1.25ppm and GC-MS; ≤ 1.25ppm).

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 packaging.

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 hypromellose, titanium dioxide, macrogol/PEG and iron oxide yellow. BSE/TSE compliance declarations were provided for all the excipients.

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

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-blistered product, consisting of four and two dosage units of nirmatrelvir 150mg tablets and ritonavir 100mg tablets, respectively, per Alu-Alu blister card.

The ritonavir 100mg tablet is identical to the HA565, the product of Hetero Labs Limited, prequalified for the treatment of HIV. The only difference is with regard to the container closure system.

Pharmaceutical development and manufacture

Nirmatrelvir 150mg tablets

The multisource product is a yellow coloured, oval shaped, bevelled edge, biconvex film coated tablet debossed with "N 15" on one side and "H" 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 tablets of the WHO recommended comparator product, Paxlovid™ (Nirmatrelvir 150mg tablets and Ritonavir 100mg tablets; co-pack by Pfizer Labs). 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 selected based on the excipients used in the comparator product and API-excipient compatibility data. Nirmatrelvir has poor flowability and direct compression may produce tablets with high weight variation and content

variability due to an uneven distribution of the API in the blend Therefore, a dry granulation (roller compaction) process was selected as the manufacturing process for the tablets. 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 nirmatrelvir tablets has no potential to contain nitrosamine impurities and hence no risk was identified.

Ritonavir100mg tablets

The multisource product is a white to off white, capsule shaped, film coated tablet debossed with 'H' on one side and 'R9' on the other side.

The aim was to develop Ritonavir 100mg tablets, bioequivalent to the WHO recommended comparator product NORVIR® Tablets 100 mg, with acceptable physicochemical properties, stability, and ease of manufacture. Ritonavir premix is prepared at the API site and delivered to the FPP site for further processing which includes a hot melt extrusion process. The premix, which is considered an intermediate for the tproduct, contains ritonavir in the amorphous form, obtained through dissolving in an organic solvent followed by stripping of the solvent. Blending of the premix with excipients and direct compression was not regarded feasible since the trial batches differed in dissolution profiles from the comparator product. Finally the hot melt extrusion step was introduced, rendering tablets with acceptable dissolution profiles. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation studies demonstrated the consistency of the process and the quality of the product.

Specifications

The specifications for Nirmatrelvir 150mg tablets include tests for description, identification of APIs (HPLC and HPLC-PDA detection), average weight, water content (KF), uniformity of dosage units (content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) and microbiological examination. The test procedures have been adequately validated.

The specifications for Ritonavir100mg tablets are pharmacopoeial based and include tests for description, identification of API (HPLC, UV), average weight, water content (KF), dissolution (2-point; HPLC detection), uniformity of dosage units (by content uniformity), organic impurities (HPLC), assay (HPLC), absence of detectable API crystalline form (p-XRD), residual solvents (GC), and microbiological examination.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data showed a slight increase for some of the degradation products, though the levels stayed well within agreed limits at both storage conditions for both tablets. The absence (below detection limit) of the crystalline form of the ritonavir API in the ritonavir tablets was demonstrated by p-XRD up to 6 months at accelerated condition and up to end-of-shelf at long-term storage condition. Forced degradation studies showed that the tablets are photo stable. 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 2022 according to internationally accepted guidelines.

Study title: An open-label, balanced, randomized, two treatment, two sequence, four period, full replicate, cross-over, single oral dose bioequivalence study of Nirmatrelvir tablets 150 mg and Ritonavir tablets 100 mg (co-pack) of Hetero Labs Limited, India (dose 2 x 150 mg Nirmatrelvir tablets + 1 x 100 mg Ritonavir tablet) and Paxlovid™ (nirmatrelvir tablets 150 mg; ritonavir tablets 100 mg) (co-packaged) of Pfizer Labs (dose 2 x 150 mg nirmatrelvir tablets + 1 x 100 mg ritonavir tablet) in normal, healthy, adult, human subjects under fasting conditions (study no. BE/22/147).

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 Hetero Labs 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, full replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments 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. E221415

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 26 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 15 ng/ml for nirmatrelvir.

The study was performed with 48 participants; data generated from a total of 43 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 (*)		Reference (R) arithmetic mean ± SD (*)		log-transformed parameters	
					Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
	T1	T2	R1	R2		
t_{max} (h)	3.00 ± 1.26	2.85 ± 1.57	3.07 ± 1.34	2.75 ± 1.33	-	-
C_{max} (ng/ml)	3844 ± 1162 (3805)	4085 ± 1247	3668 ± 998 (3491)	3527 ± 991	109.0	103.2 – 115.1
AUC_{0-t} (ng.h/ml)	36603 ± 10694 (36955)	39649 ± 10209	36710 ± 9462 (35394)	36246 ± 10924	104.4	100.0 – 109.0
AUC_{0-inf} (ng.h/ml)	37431 ± 10641	40554 ± 10511	37328 ± 9536	37262 ± 11126	98.5	95.5 – 101.5

* geometric mean

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 following bioequivalence study has been performed in 2012 according to internationally accepted guidelines.

Study title: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Ritonavir 100 mg tablets of Hetero Labs Limited, India and Norvir® (ritonavir) 100 mg tablets of Abbott Laboratories, USA in healthy human adult subjects, under fasting conditions (study no. 2661/12).

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

Treatment T: Test – 1 tablet Ritonavir 100 mg
(ritonavir 100 mg)
Batch no. E120273

Treatment R: Reference – 1 tablet Norvir®
(ritonavir 100 mg)
Batch no. 023182E

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 18 samples within 24 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 ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5.1 ng/ml for ritonavir.

The study was performed with 54 participants; data generated from a total of 50 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	3.44 ± 1.28	3.61 ± 1.12	-	-
C_{max} (ng/ml)	798 ± 366 (726)	775 ± 373 (711)	102.2	93.6 – 111.6
AUC_{0-t} (ng.h/ml)	6150 ± 2589 (5670)	5931 ± 2467 (5504)	103.0	95.8 – 110.8
AUC_{0-inf} (ng.h/ml)	6536 ± 2856 (5997)	6279 ± 2589 (5825)	103.0	96.0 – 110.5

* geometric mean

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® (Abbott Laboratories).

4. Summary of product safety and efficacy

[CV012 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, Nirmatrelvir tablets 150 mg and Ritonavir tablets 100 mg (co-pack) is pharmaceutically and therapeutically equivalent and thus interchangeable with Paxlovid™ (nirmatrelvir tablets 150 mg; ritonavir tablets 100 mg) (co-packaged) of Pfizer Labs for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [CV012 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 [CV012 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV012 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV012 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 [CV012 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 [CV012 trade name], manufactured at Hetero Labs Limited, Unit III, Plot No. 22-110, IDA, Jeedimetla, Hyderabad, Telangana, 500 055, India, in the list of prequalified medicinal products.