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	[CV017 trade name]*
Manufacturer of Prequalified Product	Celltrion Pharm, Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea
Active Pharmaceutical Ingredients (APIs)	Nirmatrelvir and ritonavir
Pharmaco-therapeutic group (ATC Code)	J05AE30
Therapeutic indication	[CV017 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.

1. Introduction

[CV017 trade name] contains two active substances, nirmatrelvir and ritonavir, each in separate tablets.

[CV017 trade name] is used for treating 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.

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 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.

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

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

The API specifications include tests for appearance, identification (IR and HPLC), polymorphic form (p-XRD), water content (KF), residue on ignition, assay (HPLC), related substances (HPLC), residual solvents (GC) and particle size distribution (PSD). The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

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

Bulk ritonavir 100 mg tablets manufactured by Cipla Ltd (HA778, prequalified via the abridged procedure) is sourced for co-blistering. In this regard the application relies on HA778 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 hypromellose, titanium dioxide, macrogol/PEG and iron oxide yellow. Lactose monohydrate is from bovine origin. BSE/TSE compliance declarations were provided for all the excipients.

Other ingredients used in the ritonavir core tablet formulation include colloidal silicon dioxide, anhydrous dibasic calcium phosphate, copovidone, sorbitan monolaurate and sodium stearyl fumarate. The seal coat contains hypromellose, while the commercially sourced proprietary film-coating mixture contains titanium dioxide, hypromellose, macrogol/PEG and polysorbate 80. 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 150 mg tablets and ritonavir 100 mg tablets, respectively, per OPA/Alu/PVC-Alu blister card.

The ritonavir 100 mg tablet is identical to HA778, the product of Cipla Ltd, prequalified for the treatment of HIV. The only difference is with regard to the container closure system.

Pharmaceutical development and manufacture

Nirmatrelvir 150 mg tablets

The multisource product is a yellow to pale yellow, oval shaped, film coated tablet debossed with "CLR" on one side and "150" 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 150 mg tablets of the WHO recommended comparator product, Paxlovid™ (Nirmatrelvir 150 mg tablets and Ritonavir 100 mg 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. A dry granulation process was selected for manufacture of the tablets due to potential content uniformity problems resulting from poor flowability of the API during direct compression. 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.

Ritonavir100 mg tablets

The multisource product is a white, oval shaped, shallow, film coated tablet with "54" debossed on one side and "247" on the other side.

Specifications

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

The specifications for ritonavir 100mg tablets include tests for description, identification of API (HPLC and TLC), polymorphic identity (p-XRD), dissolution (HPLC detection), average weight, uniformity of dosage units (by content uniformity), assay (HPLC), water content (KF), related substances (HPLC), polymorphic purity (p-XRD), residual solvent (GC) 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 condition and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the co-blistered product. Stability studies have also been performed at 25°C/60%RH (zone II) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition on the bulk pack of ritonavir tablets.

The data showed a slight increase for some of the degradation products, though the levels stayed well within agreed limits at the 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 storage condition and up to end-of-shelf at long-term storage condition. Forced degradation studies showed that the co-blistered product is photostable. 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, single-dose, full replicate, crossover oral bioequivalence study of Nirmatrelvir tablets 150 mg (150 mg x 2 tablets) and Ritonavir tablets 100 mg (Test Product-T) of Celltrion, Inc. with Paxlovid™ (nirmatrelvir tablets 150 mg [150 mg x 2 tablets] and ritonavir tablets 100 mg) (Reference Product-R) in normal healthy adult human subjects under fasting conditions (study no. BE/22/047).

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 Celltrion, Inc., Republic of Korea (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. CHEBC01A
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 20 ng/mL for nirmatrelvir.

The study was performed with 48 participants; data generated from a total of 45 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)
	T1	T2	R1	R2		
t_{max} (h)	2.76 ± 1.32	2.99 ± 1.21	2.72 ± 1.21	3.07 ± 1.44	–	–
C_{max} (ng/mL)	3169 ± 963 (3111)	3339 ± 996	3236 ± 929 (3206)	3502 ± 983	97.0	92.4 – 101.9
AUC_{0-t} (ng·h/mL)	30433 ± 7144 (30545)	32578 ± 8787	30748 ± 8313 (30281)	32529 ± 8740	100.9	96.4 – 105.6
AUC_{0-inf} (ng·h/mL)	31073 ± 7107	33254 ± 8805	31666 ± 8359	33290 ± 8944	–	–

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 HA778.

4. Summary of product safety and efficacy

[CV017 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, [CV017 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Paxlovid™ (Pfzer Labs) (co-packed with Ritonavir 100 mg) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [CV017 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 [CV017 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV017 trade name] has been shown to be bioequivalent with the comparator product.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV017 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 [CV017 trade name] was acceptable for the following indication: 'for the treatment of 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 [CV017 trade name], manufactured at Celltrion Pharm, Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea in the list of prequalified medicinal products.