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	[CV020 trade name][*]
Manufacturer of Prequalified Product	Yaopharma Co., Ltd. 100 Xingguang Avenue, Renhe Town, Yubei District, Factory Bldg. No. 2, Oral solid line I Chongqing 401121, People's Republic of China
Active Pharmaceutical Ingredient(s) (API)	Nirmatrelvir, ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors, ATC code: J05AE30
Therapeutic indication	[CV020 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

[CV020 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 Ingredients (APIs)

Nirmatrelvir

Data provided in the dossier show that nirmatrelvir is a white crystalline powder. 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.

The API specifications include tests for appearance, identification (IR and HPLC), polymorphic form (p-XRD), residue on ignition, water content (KF), related substances (HPLC), residual solvents (GC),

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

benzene (GC; ≤ 2 ppm), assay (HPLC), potential genotoxic impurity (limit is in line with ICH M7) 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

Ritonavir 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 [CV020 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.

Other ingredients

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

Other ingredients used in the ritonavir core tablet formulation include copovidone, sorbitan laurate colloidal silicon dioxide, anhydrous calcium hydrogen phosphate and sodium stearyl fumarate. The commercially sourced proprietary film-coating mixture contains hydroxypropyl cellulose, titanium dioxide, polysorbate, colloidal silicon dioxide, polyethylene glycol/macrogol, hypromellose and talc. TSE/BSE 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 film-coated tablets and ritonavir 100 mg film-coated tablets, respectively, per polyamide/Alu/PVC-Alu blister card.

Pharmaceutical development and manufacture

Nirmatrelvir 150 mg film-coated tablets

The multisource product is an orange, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'Y75' debossed (stamped into) one side and is plain on the other side

The goal of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the nirmatrelvir 150 mg film-coated tablets of the WHO recommended comparator product, Paxlovid™ (nirmatrelvir 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets; co-pack by Pfizer Labs). The quality target product profile was defined based on literature review and characterization of the comparator product and critical quality attributes were identified. The excipients of the core tablets were selected based on the excipients used in the comparator product and API-excipient compatibility data. Roller compaction was selected as the granulation method, which is same as for the comparator product indicated in the EMA assessment report. 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.

Ritonavir100 mg film-coated tablets

The multisource product is a white to off-white, capsule-shaped, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'C75' debossed (stamped into) on one side and is plain on the other side.

The goal of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the ritonavir 100 mg film-coated tablets of the WHO recommended comparator product, Paxlovid™ (Nirmatrelvir 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets; co-pack by Pfizer Labs). The quality target product profile was defined based on literature review and characterization of the comparator product and critical quality attributes were identified. The excipients of the core tablets were selected based on the excipients used in the comparator product and API-excipient compatibility data. Since ritonavir is a BCS class IV API (low solubility, low permeability), to improve the dissolution and bioavailability of the FPP, a hot melt extrusion technique was used to prepare a solid dispersion so as to achieve therapeutic equivalence with regard to the comparator product. 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 FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Specifications

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

The specifications for ritonavir 100 mg film-coated tablets are pharmacopoeial based and include tests for description, identification of API (HPLC and HPLC-DAD), related substances (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), polymorphic form (p-XRD), water content, assay (HPLC) and microbial limits. The test procedures have been adequately validated

Stability testing

Stability studies have been performed at 25°C/60%RH (zone II) and 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 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 film-coated tablets was demonstrated by p-XRD up to 6 months at accelerated storage condition and up to 24 months at long-term storage condition.

Photostability 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: A randomized, open label, balanced, two treatment, four period, two sequence, single dose, full replicate, crossover bioequivalence study of ritonavir 100 mg (1 film-coated tablet) + nirmatrelvir 300 mg (2x150 mg film-coated tablets) of Yaopharma Co., Ltd., with Paxlovid (nirmatrelvir 300 mg (2 x150 mg) + ritonavir 100 mg), of Pfizer, in normal, healthy, adult, human subjects under fasting conditions (study no. ARL/22/087).

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 Shanghai Fosun Pharmaceutical Industrial, China (test drug) with the reference formulation Paxlovid™ 150 mg (co-packed with ritonavir 100 mg (Pfizer)) 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 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. 22041280

Treatment R: Reference –Paxlovid™ (2 tablets nirmatrelvir 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, Cmax and tmax for bioequivalence evaluation. Drug concentrations for nirmatrelvir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for nirmatrelvir and about 10 ng/mL for ritonavir.

The study was performed with 50 participants; data generated from a total of 48 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for nirmatrelvir and ritonavir 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)
t_{max} (h)	2.89 ± 1.22	3.16 ± 1.22	-	-
C_{max} (ng/mL)	4201 ± 1386 (3974)	4215 ± 1129 (4058)	97.9	94.1 – 102.0
AUC_{0-t} (ng.h/mL)	41915 ± 13474 (39875)	41682 ± 11325 (40214)	99.2	95.3 – 103.2
AUC_{0-inf} (ng.h/mL)	43669 ± 13927 (41596)	43079 ± 11692 (41580)	100.0	96.3 – 103.9

* geometric mean

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)	3.88 ± 1.06	4.06 ± 1.07	-	-
C_{max} (ng/mL)	918 ± 466 (784)	902 ± 416 (798)	98.3	91.4 – 105.7
AUC_{0-t} (ng.h/mL)	8714 ± 4131 (7583)	8597 ± 3668 (7691)	98.6	92.4 – 105.2
AUC_{0-inf} (ng.h/mL)	9029 ± 4266 (7890)	8945 ± 3798 (8018)	98.4	92.6 – 104.6

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding nirmatrelvir and ritonavir. 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) (co-packed with ritonavir 100 mg).

4. Summary of product safety and efficacy

[CV020 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, [CV020 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product 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 [CV020 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 [CV020 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV020 trade name] has been shown to be bioequivalent with Paxlovid™ (nirmatrelvir tablets 150 mg; ritonavir tablets 100 mg) (co-packaged) of Pfizer Labs.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV020 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 [CV020 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 [CV020 trade name], manufactured at Yaopharma Co., Ltd.,100

Xingguang Avenue, Renhe Town, Yubei District, Factory Bldg. No. 2, Oral solid line I, Chongqing 401121, People's Republic of China in the list of prequalified medicinal products.