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	[HA787 trade name][*]
Manufacturer of Prequalified Product	Shanghai Desano Bio-Pharmaceutical Co., Ltd. 1479 Zhangheng Road China (Shanghai) Pilot Free Trade Zone Shanghai 201203 P.R. China.
Active Pharmaceutical Ingredient(s) (API)	Ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors (J05AE03)
Therapeutic indication	[HA787 trade name] is indicated as a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients.

1. Introduction

[HA787 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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)

Ritonavir has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use 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 [HA787 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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 assessment 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.

Other ingredients

Other ingredients used in the core tablet formulation include copovidone, colloidal silicon dioxide, sorbitan monolaurate, dicalcium phosphate anhydrous and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, talc and titanium dioxide. TSE/BSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, oval, film-coated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has "D32" debossed (stamped into) on one side and is plain on the other side. The tablets are presented in round, opaque, white plastic (HDPE) bottles with white, childproof plastic (polypropylene) caps.

The aim of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the WHO recommended comparator product, Norvir® 100mg tablets. The quality target product profile was defined based on the properties of the API 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. Hot melt extrusion technology was selected as the manufacturing process to convert ritonavir API from crystalline to an amorphous solid dispersion form to improve the dissolution profile of the FPP. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. 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 finished product specifications are pharmacopoeial based and include tests for description, identification of API (HPLC, UV and p-XRD), assay (HPLC), related substances (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), water content (KF) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 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 provided indicated that the product is stable at these storage conditions with no apparent negative trend. 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.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Test product (T) Ritonavir 100 mg tablets of Shanghai Desano Bio-Pharmaceutical Co., Ltd., compared to Reference product (R) Norvir® (ritonavir) 100 mg tablets of Abbvie Deutschland GmbH & Co. KG Knollstraße 67061 Ludwigshafen Deutschland in normal, healthy, adult, human subjects under fed conditions (study no. ARL/22/187).

The objective of the study was to compare the bioavailability of the stated Ritonavir 100 mg tablet manufactured by/for Shanghai Desano Bio-Pharmaceutical Co., Ltd, China (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. CZE22003.
Treatment R: Reference – 1 tablet Norvir® 100 mg (ritonavir 100 mg) Batch no. 1157230.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 36h 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 ng/ml for ritonavir.

The study was performed with 36 participants; data generated from a total of 36 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)	4.48 ± 0.44	4.54 ± 0.45	–	–
C_{max} (ng/mL)	708 ± 373 (631)	766 ± 326 (707)	89.4	82.0 – 97.4
AUC_{0-t} (ng·h/mL)	6332 ± 4534 (5289)	6711 ± 4190 (5830)	90.7	85.2 – 96.6
AUC_{0-inf} (ng·h/mL)	6738 ± 4927 (5589)	7091 ± 4614 (6095)	91.7	86.5 – 97.2

The results of the study show that pre-set 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

[HA787 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, [HA787 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Norvir® 100 mg tablet (AbbVie Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA787 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 [HA787 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA787 trade name] has been shown to be bioequivalent with Norvir® 100 mg tablet (AbbVie Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA787 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 [HA787 trade name] was acceptable for the following indication: 'a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients', and would allow inclusion of [HA787 trade name], manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd, Shanghai, China, in the list of prequalified medicinal products.