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	[HA565 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited (Unit-III), 22-110, I.D.A, Jeedimetla, Hyderabad-500055, Telangana, India.
Active Pharmaceutical Ingredient(s) (API)	Ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors (J05AE03)
Therapeutic indication	[HA565 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

[HA565 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 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. The manufacture of ritonavir entails several steps and stereoselectively produces the desired stereoisomer. Polymorphic form I, characterised by the XRPD pattern, is consistently produced.

The API specifications are pharmacopoeial based and include tests for appearance, solubility, identification (IR, HPLC, XRPD), related substances (HPLC), heavy metals, water (KF), sulfated ash, assay (HPLC), specific optical rotation, residual solvents (GC) and microbiological examination.

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 core tablet formulation include copovidone, colloidal silicon dioxide, sorbitan monolaurate, dibasic calcium phosphate anhydrous and sodium stearyl fumarate. The

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

commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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 tablets are packaged in heavy weight HDPE bottles with child-resistant polypropylene caps.

The aim was to develop ritonavir 100mg tablets, bioequivalent to the WHO recommended comparator product Norvir® 100 mg tablets, 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 FPP, 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 were not considered 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 product specifications 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 (XRPD), 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 within agreed limits at both storage conditions. The absence (below detection limit) of the crystalline form of the API was demonstrated by XRPD 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 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 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 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 the 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

[HA565 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, [HA565 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Norvir® (Abbott Laboratories) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA565 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 [HA565 trade name] is used in accordance with the SmPC.

Bioequivalence
[HA565 trade name] has been shown to be bioequivalent with Norvir® (Abbott Laboratories).

Efficacy and Safety
Regarding clinical efficacy and safety, [HA565 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 [HA565 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 [HA565 trade name], manufactured at Hetero Labs Limited (Unit-III), 22-110, I.D.A, Jeedimetla, Hyderabad-500055, Telangana, India, in the list of prequalified medicinal products.