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:	[HA650 trade name]*
Manufacturer of Prequalified Product:	Hetero Labs Limited Unit III, Plot No. #22-110, IDA, Jeedimetla Hyderabad – 500055 Telangana, India
Active Pharmaceutical Ingredients (APIs):	Lopinavir & Ritonavir
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR10)
Therapeutic indication:	[HA650 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and children weighing 10 kg or more.

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

1. Introduction

[HA650 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and children weighing 10 kg or more.

[HA650 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

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)

Lopinavir

Lopinavir has four chiral centres and is known to exhibit polymorphism. The manufacture of lopinavir entails several steps and is stereoselectively producing the desired stereoisomer and the type-I highly hydrated crystal form. The API produced is soluble in organic solvents like methanol, ethanol, dichloromethane and DMF, but practically insoluble in water and of BCS low solubility in aqueous buffers across the physiological pH range. It is hygroscopic.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), crystal form (XRPD), water content (KF), specific optical rotation, residue on ignition, heavy metals, related substances (HPLC), assay (HPLC) and residual solvents (GC).

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.

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 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), related substances (HPLC), heavy metals, water content (KF), sulfated ash, assay (HPLC), crystal form (XRPD), specific optical rotation, residual solvents (GC), microbial limits and genotoxic impurities (UFLC-MS and GC-MS).

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 and sodium stearyl fumarate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol, hydroxypropyl cellulose, iron oxide yellow, talc, colloidal anhydrous silica and polysorbate. TSE / BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, capsule shaped, biconvex film-coated tablet, debossed with 'H' on one side and 'L7' on the other side. The tablets are packaged in HDPE bottles with child resistant closures.

Two tablet strengths of lopinavir/ritonavir tablets (200 mg/50 mg and 100 mg/25 mg), proportionally similar in composition and manufactured according to the same procedure, were developed. The

development focussed on the higher strength.

The development of the final composition of the tablets has been described. The objective was to develop a stable product, bioequivalent to the comparator product, Kaletra® 200 mg/ 50 mg Tablets. The tablets have been developed as a solid dosage form for oral administration. The excipients of the core tablet are qualitatively similar to those of the comparator product. Lopinavir and ritonavir are practically insoluble in water. Hot melt extrusion technology was considered as an effective way of manufacturing tablets for poorly soluble APIs and hence it was selected by the manufacturer to obtain the APIs in the solid dispersible form. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data demonstrated the consistency of the process and the quality of the product.

Comparative in-vitro dissolution studies showed that Lopinavir/Ritonavir 100 mg/25 mg Tablets have similar in vitro dissolution characteristics to the higher strength, which was used in bioequivalent studies.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), water content (KF), average mass, dissolution (HPLC detection; 2-point for both APIs), uniformity of dosage units (by content uniformity), related compounds (HPLC), assay (HPLC), microbiological examination and XRPD (for detection of API crystalline forms). The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/ 75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data showed little change with time and were well within the agreed specifications at both storage conditions. No change in the solid state form of the APIs could be detected. 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 was performed in 2009 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single-dose bioequivalence study of Lopinavir and Ritonavir 200 mg/50 mg Tablets (containing lopinavir 200 mg and ritonavir 50 mg) of Hetero Drugs Limited, India comparing with Kaletra® (containing lopinavir 200 mg and ritonavir 50 mg) tablets manufactured by Abbott Laboratories, North Chicago, IL 60064, U.S.A, in healthy, adult human subjects, under fasting conditions (study no. CR-BE-253-LORI-2008).

The objective of the study was to compare the bioavailability of the stated Lopinavir and Ritonavir 200 mg/50 mg Tablets fixed-dose combination tablet manufactured by Hetero Drugs Limited, India (test drug) with the same dose of the reference formulation (Kaletra®, Abbott Laboratories) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T:	Test – 1 tablet Lopinavir/Ritonavir 200 mg/50 mg (lopinavir 200 mg + ritonavir 50 mg) Batch no. E8044.

Treatment R: Reference – 1 tablet Kaletra®
(lopinavir 200 mg + ritonavir 50 mg)
Batch no. 61564AA40.

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 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 lopinavir and ritonavir were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng / mL for lopinavir and about 5 ng / mL for ritonavir.

The study was performed with 44 participants; data generated from a total of 41 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lopinavir and ritonavir as well as statistical results are summarised in the following tables:

Lopinavir

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)	3.63 ± 0.89	3.36 ± 1.16	-	-
C_{max} (µg/mL)	3.67 ± 1.28 (3.42)	3.88 ± 1.50 (3.60)	95.8	86.9–105.7
AUC_{0-t} (µg.h/mL)	34.9 ± 15.4 (30.8)	37.2 ± 18.0 (33.1)	94.0	84.5–104.5
AUC_{0-inf} (µg.h/mL)	37.6 ± 18.3 (32.8)	39.9 ± 20.7 (35.2)	94.0	84.6–104.5

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)	3.51 ± 1.12	3.12 ± 1.29	-	-
C_{max} (µg/ml)	181 ± 78 (164)	196 ± 101 (171)	96.9	87.0–108.0
AUC_{0-t} (µg.h/ml)	1373 ± 709 (1180)	1417 ± 732 (1222)	97.5	88.7–107.1
AUC_{0-inf} (µg.h/ml)	1511 ± 833 (1292)	1544 ± 808 (1331)	98.1	89.7–107.2

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and Cmax values regarding lopinavir and ritonavir. Accordingly, the test fixed-dose combination tablet Lopinavir and Ritonavir 200 mg/50 mg Tablets meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Kaletra® (Abbott Laboratories, USA).

A biowaiver was granted for the 100/25 mg FDC tablet strength (Hetero Laboratories Limited, India) in accordance with WHO guidelines. In comparison with the strength of the test product used in the bioequivalence study (200/50 mg; see WHOPAR HA492), the lopinavir/ritonavir 100/25 mg FDC tablet was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be comparable.

4. Summary of Product Safety and Efficacy

According to the submitted data on quality [HA650 trade name] is a direct scale-down of Lopinavir/Ritonavir 200 mg/50 mg Tablets. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Kaletra® for which benefits have been proven in terms of virological and immunological efficacy. The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made 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 [HA650 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA650 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence [HA650 trade name] and Kaletra® (Abbot Laboratories, USA) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA650 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA650 trade name] was acceptable for the following indication: **"for the treatment of HIV-1 in combination with other antiretroviral agents in adults and children weighing 10 kg or more "** and has advised that the quality, efficacy and safety of [HA650 trade name] allow inclusion of [HA650 trade name], manufactured at Hetero Labs Limited, Unit III, #22-110, IDA, Jeedimetla, Rangareddy District, Hyderabad – 500055, Telangana, India, in the list of prequalified medicinal products.