SCIENTIFIC DISCUSSION

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.

Name of the Finished Pharmaceutical Product:	[HA492 trade name] *
Manufacturer of Prequalified Product:	Hetero Labs Limited Unit – III No. 22-110, I.D.A., Jeedimetla Hyderabad, 500 055 Telangana India
Active Pharmaceutical Ingredients (APIs):	Lopinavir + Ritonavir
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, protease inhibitors (J05AE06 and J05AE03).
Therapeutic indication:	[HA492 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus Type 1 (HIV-1) infected adults.

1. Introduction

[HA492 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredients (APIs)

Lopinavir and ritonavir

Lopinavir and ritonavir are class 4/2 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms).

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 is stereoselectively producing 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, related substances (HPLC), heavy metals, water, sulphated ash, assay (HPLC), crystal form (XRPD), specific optical rotation, residual solvents and microbiological examination.

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

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.

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 in aqueous buffers across the physiological pH range, and is hygroscopic.

The API specifications include tests for description, solubility, identification, crystal form (XRPD), water content, specific optical rotation, residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), residual solvents 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 colloidal anhydrous silica, copovidone, sodium stearyl fumarate and sorbitan laurate. The film coating contains colloidal anhydrous silica, hydroxypropyl cellulose, hypromellose, iron oxide yellow, polyethylene glycol, polysorbate 80, talc and titanium dioxide.

Finished Pharmaceutical Product (FPP)

Product specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), water content, average mass, uniformity of dosage units (by content uniformity), dissolution, related compounds (HPLC), assay (HPLC), microbiological examination and XRPD (for detection of API crystalline forms).

Pharmaceutical development

[HA492 trade name] is a yellow, film-coated, ovaloid tablet debossed with ‘H’ on one side and ‘70’ on other side. The tablets are packaged in Alu-Alu strips and PVC/PVDC-Alu blisters and in HDPE bottles closed with polypropylene ribbed cap with continuous threading with pulp liners.

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 solid dosage form for oral administration. The excipients of the core tablet are qualitative similar to those of the comparator product. Lopinavir and ritonavir are practically insoluble in water. Hot melt extrusion technology was considered 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. The conditions of the hot melt extrusion have been optimised in light of the stability of ritonavir. 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 the multisource product has similar in vitro dissolution characteristics to Kaletra® 200 mg/50 mg tablets. It has furthermore been demonstrated that the multipoint dissolution characteristics of the multisource product are retained during the shelf life.

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 all packaging configurations 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 has been 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 [HA492 trade name] (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 [HA492 trade name] 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 [HA492 trade name] (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 (*)	Reference (R) arithmetic mean ± SD (*)	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·hour/mL)	34.9 ± 15.4 (30.8)	37.2 ± 18.0 (33.1)	94.0	84.5–104.5
AUC_{0-inf} (µg·hour/mL)	37.6 ± 18.3 (32.8)	39.9 ± 20.7 (35.2)	94.0	84.6–104.5

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

* geometric mean

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding lopinavir and ritonavir. Accordingly, the test fixed-dose combination tablet [HA492 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Kaletra® (Abbott Laboratories, USA).

4. Summary of Product Safety and Efficacy

[HA492 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [HA492 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference 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 [HA492 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA492 trade name] has shown to be bioequivalent with Kaletra® (Abbott Laboratories).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA492 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 assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA492 trade name] was acceptable for the following indication: “for the treatment of HIV-1 infected adults in combination with other antiretroviral agents” and has advised that the quality, efficacy and safety of [HA492 trade name] allow inclusion of [HA492 trade name], manufactured at Hetero Labs Limited, Unit III, No. 22-110, I.D.A, Jeedimetla, Hyderabad 500 055, Andhra Pradesh, India, in the list of prequalified medicinal products.