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	[HA760 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, India
Active Pharmaceutical Ingredient(s) (API)	Lopinavir/Ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR10)
Therapeutic indication	[HA760 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.

1. Introduction

[HA760 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.

The choice of [HA760 trade name] to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and their treatment history (see sections 4.4 and 5.1).

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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)

Lopinavir

Lopinavir is described in the Ph.Int, Ph.Eur, BP and USP. Lopinavir is a white to off-white powder. The pharmaceutical form is (2S)-N-[(1S,3S,4S)-1-benzyl-4-[[2-(2,6-dimethylphenoxy) acetyl]-amino]-3-hydroxy-5-phenylpentyl]-3-methyl-2-[2-oxotetrahydro-pyrimidin-1(2H)-yl] butanamide. Lopinavir is practically insoluble in water.

Lopinavir exhibits polymorphism. The 'type-1 highly hydrated crystal form' is consistently produced by the manufacturer and controlled by x-ray powder diffraction (p-XRD).

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

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), polymorphic form (p-XRD), water content, specific optical rotation, residue on ignition, 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 packing material.

Ritonavir

Ritonavir is described in the Ph.Int, Ph.Eur, BP 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 stereo selectively produces the desired stereoisomer. Polymorphic form I, characterised by the XRD pattern, is consistently produced.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), polymorphic form (p-XRD), water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limits and genotoxic impurities (UFLC-MS; and GC; ≤ 1.25ppm).

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 silicon dioxide, copovidone, sorbitan monolaurate, microcrystalline cellulose, crospovidone and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol, talc and iron oxide yellow. None of the excipients are of animal or human origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pale yellow, oblong shaped, film coated tablet debossed with ‘C 29’ on one side and plain on the other. The tablets are packaged in a white, opaque HDPE bottle and closed with either a white, round polypropylene child resistant cap and a head induction foil inner seal or a white, round polypropylene screw cap.

Two strengths of lopinavir/ritonavir tablets proportionally similar in composition were developed: 100mg/25mg and 200mg/50mg.The development focused on the higher strength, which was used in the BE study against the WHO recommended comparator product Kaletra® (lopinavir/ritonavir) 200 mg/50 mg tablets. Once the formulation for the higher strength was finalized, the lower strength formulation was pursued using dose-proportionality approach.

The aim of the development was to formulate an immediate release FDC dosage form. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The selection of excipients was based on the comparator product and API-excipient compatibility studies. The manufacturing process involves conversion of the poorly soluble crystalline forms of the two APIs to amorphous forms via the hot melt extrusion process (solid-solid dispersion technique), thereby improving their solubility, which is important for bioavailability.

Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain coated tablets of desired characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and PDA detector) and colorants, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), elemental impurities, polymorphic identification of the APIs (p-XRD) and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30ºC/75%RH as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are regarded acceptable. The in-use storage period after first opening of the bottle is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

Study title:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study of Lopinavir and Ritonavir tablets USP 200 mg/50 mg (2 tablets x 200 mg / 50 mg, i.e. 400 mg / 100 mg dose) of Micro Labs Limited, India comparing with that of Kaletra® (lopinavir/ritonavir) tablets 200 mg/50 mg (2 tablets x 200 mg / 50 mg, i.e. 400 mg / 100 mg dose) of AbbVie Ltd., Barceloneta, Pr 00617 in normal, healthy, adult, human subjects under fasting conditions. (study no. 0722-19).

The objective of the study was to compare the bioavailability of the stated Lopinavir/Ritonavir 200/50 mg FDC tablet manufactured by Micro Labs Limited, India (test drug) with the reference formulation Kaletra® (lopinavir/ritonavir) tablet 200/50 mg (AbbVie Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 2 tablets Lopinavir/Ritonavir 200/50 mg (lopinavir 400 mg + ritonavir 100 mg) Batch no. : OBBG001
Treatment R:	Reference – 2 tablets Kaletra® 200/50 mg (lopinavir 400 mg + ritonavir 100 mg) Batch no. 1086417

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, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lopinavir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/ml for lopinavir and about 2.5 ng/ml for ritonavir.

The study was performed with 62 participants; data generated from a total of 57 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)	4.00	4.33	–	–
C_{max} (ng /mL)	8337 ± 2382 (8033)	8035 ± 2834 (7542)	106.5	100.8 – 112.5
AUC_{0-t} (ng·h/mL)	106322 ± 39544 (99538)	100616 ± 43348 (91051)	109.3	102.3 – 116.9
AUC_{0-inf} (ng h/mL)	109567 ± 40477 (102715)	103073 ± 44176 (93338)	110.0	103.0 – 117.6

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)	4.00	4.33	–	–
C_{max} (ng /mL)	670 ± 393 (579)	607 ± 347 (511)	113.4	103.5 – 124.3
AUC_{0-t} (ng·h/mL)	5290 ± 2717 (4694)	4806 ± 2559 (4144)	113.3	105.3 – 121.9
AUC_{0-inf} (ng h/mL)	5387 ± 2758 (4783)	4902 ± 2584 (4240)	112.8	105.0 – 121.1

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 Lopinavir/Ritonavir 200/50 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Kaletra® 200/50 mg tablet (AbbVie Ltd.).

A biowaiver was granted for the additional 100/25 mg FDC tablet strength (Micro Labs Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the lopinavir/ritonavir 100/25 mg FDC tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of product safety and efficacy

According to the submitted data on quality, 1opinavir/ritonavir 100/25 mg FDC tablets in [HA760 trade name] is a direct scale-down of 200/50 mg FDC tablets (Micro Labs Limited, India). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product lopinavir/ritonavir tablets 200 mg/50 mg (AbbVie Ltd., Barceloneta) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA760 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 [HA760 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA760 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA760 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 [HA760 trade name] was acceptable for the following indication: '**treatment of human immunodeficiency virus (HIV-1) infection in adults and children weighing 10 kg or more** ', and would allow inclusion of [HA760 trade name], manufactured at Micro Labs Limited, Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, India, in the list of prequalified medicinal products.