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	[HA697 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited F4 & F12, MIDC, Malegaon Sinnar, Nashik – 422 113 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Lopinavir and Ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR10)
Therapeutic indication	[HA697 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in infants and children patients14 days and older, weighing over 3 kg.

1. Introduction

[HA697 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in infants and children patients14 days and older, weighing over 3 kg.

[HA697 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 Ingredient (API)

Lopinavir and ritonavir have 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 APIs, used in the manufacture of [HA697 trade name], are of good

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

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.

Other ingredients

Other ingredients used in the granules for oral suspension include copovidone, sorbitan monolaurate, colloidal silicon dioxide, ethyl cellulose, mannitol, acesulfame potassium, sodium stearyl fumarate and vanilla flavour. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to creamish granular powder filled in a sachet.

The development of the final composition of the granules for oral suspension has been described. The objective was to develop a stable product; bioequivalent to the WHO recommended comparator product, Kaletra® oral solution (lopinavir/ritonavir 80 mg/20 mg per mL). The excipients selected were based on literature information, API-excipient compatibility studies and prior experience of manufacturing similar types of immediate release solid oral dosage forms.

Lopinavir and ritonavir are practically insoluble in water. To improve upon the solubility of the two APIs, hot melt extrusion technology was used to prepare the lopinavir premix blend and ritonavir premix blend as two separate parts, which were then compacted, milled and blended together. The blend was finally filled in sachets. 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.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), water content (KF), PXRD and microbial limits.

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. The product proved to be quite stable at these conditions, with PXRD showing apparent retention of the amorphous forms of the 2 APIs. 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 2017 according to internationally accepted guidelines:

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Lopinavir/Ritonavir granules (2 sachets X 40/10 mg) 40 mg/10 mg of Mylan Laboratories Limited, India with Kaletra® (lopinavir/ritonavir) oral solution 80mg/20mg per ml of AbbVie Inc., North Chicago, IL 60064 USA, in normal healthy adult human subjects under fed conditions (study no. C16212).

The objective of the study was to compare the bioavailability of the stated Lopinavir/Ritonavir 40mg/10mg granules manufactured by Mylan Laboratories Limited, India (test drug) with the reference formulation Kaletra® (AbbVie Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, 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 – 2 sachets Lopinavir/Ritonavir 40mg/10mg granules (lopinavir 80 mg + ritonavir 20 mg) Batch no. 201897.

Treatment R: Reference – 1 ml Kaletra® 80mg/20mg oral solution (lopinavir 80 mg + ritonavir 20 mg) Batch no. 1043600

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 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 3 ng/mL for lopinavir and 0.1 ng/mL for ritonavir.

The study was performed with 72 participants; data generated from a total of 68 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)	5.46 ± 1.53	6.24 ± 2.82	–	–
C_{max} (ng/mL)	482 ± 328 (390)	490 ± 371 (370)	105.4	94.2 – 117.9
AUC_{0-t} (ng·h/mL)	4404 ± 3491 (3145)	4493 ± 3906 (2955)	106.4	94.5 – 119.9
AUC_{0-inf} (ng·h/mL)	4490 ± 3584 (3216)	4721 ± 4089 (3077)	104.5	92.6 – 118.0

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)	4.89 ± 0.54	5.20 ± 1.10	–	–
C_{max} (ng/mL)	31 ± 16 (28)	30 ± 18 (25)	110.4	100.9 – 120.7
AUC_{0-t} (ng·h/mL)	266 ± 153 (220)	263 ± 176 (202)	108.7	98.5 – 119.9
AUC_{0-inf} (ng·h/mL)	275 ± 160 (226)	273 ± 186 (209)	108.4	98.4 – 119.4

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 40 mg/10 mg granules meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Kaletra® (AbbVie Inc.).

4. Summary of product safety and efficacy

[HA697 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, [HA697 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Kaletra® (AbbVie Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA697 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 [HA697 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA697 trade name] has been shown to be bioequivalent with Kaletra® (AbbVie Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA697 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 [HA697 trade name] was acceptable for the following indication: '**for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in infants and children patients14 days and older, weighing over 3 kg**' and would allow inclusion of [HA697 trade name], manufactured at Mylan Laboratories Limited, F4 & F12, MIDC, Malegaon, Sinnar, Nashik – 422 113, Maharashtra, India, in the list of prequalified medicinal products.