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	[HA574 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block No.: 2, Village Theda P.O. Lodhi Majra Tehsil Baddi Distric.: Solan Himachal Pradesh, 174101 India
Active Pharmaceutical Ingredient(s) (API)	Lopinavir and ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR10)
Therapeutic indication	[HA574 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

[HA574 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.

[HA574 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

Lopinavir has four chiral centres and is known to exhibit polymorphism. The manufacture of lopinavir entails several steps and is stereo-selectively 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. It is slightly hygroscopic.

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

The API specifications include tests for description, solubility, identification (IR, HPLC), water content, residue on ignition, heavy metals, organic impurities (HPLC), assay (HPLC), crystal form (XRPD), specific optical rotation and residual solvents.

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 stereo-selectively 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 description, solubility, identification (IR, HPLC), heavy metals, water, residue on ignition, organic impurities (HPLC), assay (HPLC), crystal form (XRPD), specific optical rotation and residual solvents.

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, sorbitan monolaurate, colloidal silicon dioxide, anhydrous dibasic calcium phosphate and sodium stearyl fumarate. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-part hydrolysed, titanium dioxide, polyethylene glycol, talc and iron oxide yellow. TSE / BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, capsule shaped, biconvex, film-coated tablet debossed with “M32” on one side and plain on the other side. The tablets are packaged in a heavy weight HDPE bottle with polypropylene child-resistant closure, also containing 2 sachets each filled with 1 gm silica gel.

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® 200mg/50mg Tablets. The tablets have been developed as solid dosage form for oral administration. As reported in literature, lopinavir and ritonavir are practically insoluble in water, to such an extent that when administered as tablet prepared by conventional techniques, the oral bioavailability is negligible. In order to have clinically significant concentrations of these APIs, tablets containing the lopinavir and lopinavir in solid dispersion form were developed. Different techniques to prepare the solid dispersion (solubilisation of the APIs and adsorbing them on solid material, co-precipitation and solvent evaporation) were explored during development. Based on development studies, the solvent evaporation technique was selected**.** Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Comparative *in-vitro* dissolution studies showed that the multisource product has similar in vitro dissolution characteristics to Kaletra 200mg/50mg tablets in the media studied. It has furthermore been demonstrated that the multipoint dissolution characteristics of the multisource product and the amorphous nature of the APIs are retained during shelf life.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC, TLC), average weight, dissolution (2 point; HPLC detection), uniformity of dosage units (by content uniformity), organic impurities (HPLC), assay (HPLC), water content, residual solvents, microbial enumeration and specified microorganisms and XRPD (for detection of API crystalline forms).

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 has been performed in 2012 according to internationally accepted guidelines.

Bioequivalence study of two tablets as single dose of fixed dose combination of Lopinavir and Ritonavir tablets 200 mg / 50 mg (each tablet contains lopinavir USP 200 mg and ritonavir USP 50 mg) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with two tablets of Kaletra® (lopinavir/ ritonavir) tablets 200 mg / 50 mg (each tablet contains 200 mg lopinavir and 50 mg ritonavir) manufactured for Abbott Laboratories, USA in healthy, adult, human subjects under fasting condition (study no. BEQ-806-LR(F)-2011).

The objective of the study was to compare the bioavailability of the stated Lopinavir/Ritonavir 200mg/50mg FDC tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with 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 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 200mg/50 mg
(lopinavir 400 mg + ritonavir 100mg)
Batch no. BLW202A.

Treatment R: Reference – 2 tablets Kaletra®
(lopinavir 400 mg + ritonavir 100mg)
Batch no. 08411AA

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 48h 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 202 ng/ml for lopinavir and about 15 ng/ml for ritonavir.

The study was performed with 72 participants; data generated from a total of 63 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine and tenofovir 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)	3.70 ± 0.92	3.81 ± 1.05	-	-
C_{max} (ng/mL)	7669 ± 2095 (7386)	7727 ± 1784 (7537)	98.0	93.1 – 103.2
AUC_{0-t} (ng.h/mL)	102339 ± 37491 (95807)	101239 ± 34535 (96090)	99.7	93.6 – 106.2
AUC_{0-inf} (ng.h/mL)	110837 ± 40784 (103554)	109720 ± 36669 (104104)	99.5	93.5 – 105.8

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)	3.75 ± 0.90	3.60 ± 1.04	-	-
C_{max} (ng/mL)	633 ± 323 (554)	609 ± 285 (551)	100.5	91.8 – 110.0
AUC_{0-t} (ng.h/mL)	5197 ± 2413 (4644)	5090 ± 2217 (4651)	99.8	92.9 – 107.3
AUC_{0-inf} (ng.h/mL)	5474 ± 2496 (4909)	5347 ± 2252 (4908)	100.0	93.4 – 107.2

Conclusions:

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

4. Summary of product safety and efficacy

[HA574 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, [HA574 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Kaletra® (Abbot Laboratories, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA574 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 [HA574 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA574 trade name] has been shown to be bioequivalent with Kaletra® (Abbot Laboratories, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA574 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 [HA574 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 would allow inclusion of [HA574 trade name], manufactured at Macleods Pharmaceuticals Limited, Block No.: 2, Village Theda, P.O. Lodhi Majra, Tehsil Baddi, District Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.