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	[HA763 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited (ML06) 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)	Abacavir/Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR02)
Therapeutic indication	[HA763 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in children weighing at least 3 to 25 kg.

1. Introduction

[HA763 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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)

Abacavir sulfate

Based on scientific principles WHO PQTm has identified abacavir (as sulfate) (up to 600 mg oral dose) as a BCS class 3 API. The API is thus highly soluble over the pH range 1 to 6.8.

The APIMF of abacavir sulfate, (1S,4R)-4-[2-Amino-6(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1), has been accepted through WHO's APIMF procedure. The manufacture of abacavir sulfate, which contains two chiral carbon atoms, entails several chemical steps. The desired stereochemistry at the chiral centres (1S,4R) is built into a starting material. The

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

reactions involved in the conversion of this starting material to the API do not involve the chiral centres and hence the original chirality of the starting material is retained throughout the synthesis.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC and test for sulfate), water content (KF), residue on ignition, content of sulfate (potentiometric), organic impurities (HPLC), enantiomer content (HPLC; ≤ 0.20%), assay (HPLC), residual solvents (GC), a nitroso impurity (HPLC; ≤ 2.5 ppm), and particle size distribution.

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.

Lamivudine

Based on scientific principles WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble. Lamivudine API is described in the Ph. Int, Ph. Eur and USP, and is considered well-established in the WHO PQTm.

The API specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR and HPLC), light absorption, water content (KF), limit of lamivudine enantiomer (HPLC; ≤ 0.30%), residual solvents (GC), related substances (HPLC), assay (HPLC), residue on ignition, bulk density, particle size distribution, specific optical rotation, mesylates content (HPLC; each ≤ 5 ppm) and tosilates content (GC; each ≤ 5 ppm).

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.

Other ingredients

Other ingredients used in the dispersible tablet formulation include, microcrystalline cellulose, sodium starch glycolate, sucralose, crospovidone, magnesium stearate and strawberry flavour. The commercially sourced proprietary strawberry flavour which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. None of the excipients are of animal or human origin. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white coloured, oval-shaped, biconvex, uncoated dispersible tablet, scored on one side, debossed with ‘8’ on one half and ‘0’ on other half and score line on the other side. The score line is intended for subdivision of tablets when a half-tablet dose is to be administered. The tablets are packaged in a white, opaque, HDPE bottle with a canister of 3g silica gel and purified cotton and closed with a white, round, polypropylene child-resistant cap with a head induction foil inner seal.

The objective of the product development was to obtain a stable and robust formulation, bioequivalent to the WHO recommended comparator product, Epzicom® tablets. The excipients were selected with reference to the comparator product. The flavouring agent and sweetener were included to improve the taste of the paediatric formulation. Compatibility studies which were conducted showed that the APIs were compatible with the selected excipients. Wet granulation process was selected to manufacture the finished pharmaceutical product due to the poor flow properties of the APIs. Based on 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.

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 APIs (HPLC and TLC), water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), disintegration time, fineness of dispersion, subdivision of tablets, assay (HPLC), related substances (HPLC), residual solvents, elemental impurities and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable, with no significant change or negative trend observed. 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 2019 according to internationally accepted guidelines.

Study title: A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover, oral bioequivalence study of abacavir and lamivudine dispersible tablets 120/60 mg (dose = 1*5 tablets) manufactured by Micro Labs Limited, India with Epzicom® (abacavir 600 mg and lamivudine 300 mg) tablets (dose= 1 tablet) of ViiV Healthcare, Research Triangle Park, NC 27709 in healthy, adult, human subjects under fasting conditions (study no. 034-19).

The objective of the study was to compare the bioavailability of the stated abacavir/lamivudine 120mg/60 mg FDC tablet manufactured for/by Micro Labs Limited, India (test drug) with the reference formulation Epzicom® 600/300 mg (ViiV Healthcare) 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 treatments in a randomized fashion:

Treatment T:	Test – 5 tablets abacavir/lamivudine 120mg/60 mg (abacavir 600 mg + lamivudine 300 mg) Batch no. : AUBG001
Treatment R:	Reference – 1 tablet Epzicom® 600/300 mg (abacavir 600 mg + lamivudine 300 mg) Batch no. 7ZP4949

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 samples within 36 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 abacavir and lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for abacavir and about 25 ng/mL for lamivudine.

The study was performed with 32 participants. Data generated from a total of 31 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Abacavir

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)	0.88 ± 0.49	1.07 ± 0.58	-	-
C_{max} (ng/mL)	8229 ± 2196 (7988)	8063 ± 1792 (7866)	101.6	92.5 – 111.5
AUC_{0-t} (ng.h/mL)	20306 ± 3921 (19962)	20708 ± 4194 (20297)	98.4	95.3 – 101.5
AUC_{0-inf} (ng.h/mL)	20582 ± 4041 (20223)	20959 ± 4230 (20542)	98.5	95.5 – 101.5

* geometric mean

Lamivudine

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)	2.04 ± 0.94	1.62 ± 0.63	-	-
C_{max} (ng/mL)	3062 ± 724 (3329)	3407 ± 766 (2972)	112.0	102.7 – 122.2
AUC_{0-t} (ng.h/mL)	16507 ± 3563 (16692)	16957 ± 3093 (16099)	103.7	96.6 – 111.3
AUC_{0-inf} (ng.h/mL)	16890 ± 3431 (17000)	17261 ± 3095 (16533)	102.8	96.3 – 109.8

* geometric mean

The results of the study show that the preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding abacavir and lamivudine. Accordingly, the test abacavir/lamuvidine 120mg/60 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the reference Epzicom® (ViiV Healthcare).

4. Summary of product safety and efficacy

[HA763 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, [HA763 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epzicom® (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA763 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 [HA763 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA763 trade name] has been shown to be bioequivalent with Epzicom® (ViiV Healthcare).

Efficacy and Safety
Regarding clinical efficacy and safety, [HA763 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 [HA763 trade name] was acceptable for the following indication: **treatment of human immunodeficiency virus (HIV) infection in children weighing at least 3 to 25 kg**, **in combination with other antiretroviral agents,** and would allow inclusion of [HA763 trade name], manufactured at Micro Labs Limited (ML06), 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.