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:	[HA740 trade name][1]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block N2, Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient (API):	Abacavir (as sulfate)/Lamivudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR02)
Therapeutic indication:	[HA740 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

1. Introduction

[HA740 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg. [HA740 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)

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 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, organic

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

impurities (HPLC), enantiomer content (HPLC; ≤ 0.20%), a nitroso impurity (HPLC; ≤ 2.5 ppm), assay (HPLC), content of sulfate (potentiometric), residual solvents (GC) and particle.

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, identification (IR and HPLC), light absorption, melting point, water content (KF), limit of lamivudine enantiomer (HPLC; ≤ 0.30 %), related substances (HPLC), assay (HPLC), residual solvents (GC), bulk density, particle size, residue on ignition, specific optical rotation, tosilates content (HPLC; each ≤ 5 ppm) and mesylates 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 core tablet formulation include, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, polysorbate 80, titanium dioxide and FD& C yellow #6/Sunset yellow FCF aluminium lake. 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 an orange-coloured, modified capsule-shaped, biconvex, film-coated tablet, with deep break line on one side and plain on other side. The tablets are packaged in either a white, round, HDPE bottle with a sachet of 1 g carbon/silica blend and closed with polypropylene child resistant closure with pulp and white printed heat seal liner or a Alu/Alu-PVC blister card.

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. Compatibility studies which were conducted showed that the APIs were compatible with the selected excipients. Formulation trials were performed to optimise the concentration of excipients and process parameters. Wet granulation process using organic solvent was selected to manufacture the finished pharmaceutical product due to the poor flow and high concentration of the APIs. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of APIs (HPLC, UV) and colourants, dissolution (HPLC detection), uniformity of dosage units (by weight variation for abacavir and content uniformity for lamivudine), organic impurities (HPLC), assay (HPLC), subdivision of tablets, loss on drying, residual solvent 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 2018 according to internationally accepted guidelines.

Study title: Single-dose fasting in vivo bioequivalence study of fixed dose combination of Abacavir and Lamivudine tablets USP 600 mg /300 mg (Macleods Pharmaceuticals Ltd., India) to Epzicom® (abacavir and lamivudine) tablets 600 mg/ 300mg (GlaxoSmithKline, USA) in healthy, adult, human subjects (study no. BEQ-1758-AbLa (F)-2016).

The objective of the study was to compare the bioavailability of the stated Abacavir/Lamivudine 600/300 mg FDC tablet manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Epzicom® 600/300 mg (GlaxoSmithKline) 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 – 1 tablet Abacavir/Lamivudine 600/300 mg (abacavir 600 mg + lamivudine 300 mg) Batch no.: BAJ5702B
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 23 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 abacavir and lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 75 ng/mL for abacavir and about 50 ng/mL for lamivudine.

The study was performed with 24 participants; data generated from a total of 23 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)[#]	1.24 ± 0.51	1.35 ± 0.60	-	-
C_{max} (ng/mL)	6592 ± 1440 (6430)	6386 ± 1307 (6262)	102.7	95.0 – 111.1
AUC_{0-t} (ng.h/mL)	17389 ± 3864 (16981)	17289 ± 3872 (16901)	100.5	95.4 – 105.8
AUC_{0-inf} (ng.h/mL)	17774 ± 3925 (17359)	17679 ± 3857 (17300)	100.3	95.4 – 105.5

* 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)[#]	1.73 ± 0.58	2.10 ± 0.80	-	-
C_{max} (ng/mL)	2891 ± 737 (2795)	2843 ± 755 (2727)	102.5	95.2 – 110.4
AUC_{0-t} (ng.h/mL)	14688 ± 4316 (14057)	15117 ± 4229 (14471)	97.1	89.7 – 105.1
AUC_{0-inf} (ng.h/mL)	15049 ± 4311 (14435)	15485 ± 4210 (14868)	97.1	90.0 – 104.8

* 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 abacavir and lamivudine. Accordingly, the test Abacavir/Lamuvidine 600/300 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® (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA740 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 [HA740 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epzicom® for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered acceptable when guidance and restrictions as stated in the summary of product characteristics are taken into account. 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 [HA740 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA740 trade name] has been shown to be bioequivalent with Epzicom® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA740 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA740 trade name] was acceptable for the following indication: **"in combination with other antiretroviral agents for the treatment of HIV infection in adults, adolescents and children weighing at least 25 kg, "**and would allow inclusion of [HA740 trade

name], manufactured Macleods Pharmaceuticals Limited ,Block N2, Village Theda, Tehsil Baddi, Dist. Solan, Himachal Pradesh, India, in the list of prequalified medicinal products.