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	[HA657 trade name]*
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit – V Sy No. 439, 440, 441 & 458 TSIIC Formulation SEZ Polepally (V), Jadcherla (M) Mahaboobnagar District Telangana, India
Active Pharmaceutical Ingredient(s) (API)	Abacavir (as sulfate)/Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR02)
Therapeutic indication	[HA657 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

[HA657 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.

[HA657 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, the WHO Prequalification Team – Medicines (PQTm) has identified abacavir (as sulfate) (up to 600mg oral dose) as a BCS class III API. The API is thus regarded highly soluble in terms of the BCS.

The APIMF of abacavir sulfate, (1*S*, 4*R*)-4-[2-Amino-6(cyclopropylamino)-9*H*-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 counter ion), water content (KF), residue on ignition, heavy metals, content of sulfate (potentiometric), organic impurities (HPLC), assay (HPLC), enantiomer content (chiral HPLC; ≤ 0.20%), residual solvents (GC) and particle size. Cyclopropylamine is controlled at a limit of 30 ppm (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.

Lamivudine

Based on scientific principles WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus regarded highly soluble in terms of the BCS.

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, HPLC), light absorption, water content (KF), specific optical rotation, residue on ignition, heavy metals, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), residual solvents (GC), chromatographic purity (HPLC), assay (HPLC), particle size, methane sulfonates (GC-MS; each ≤ 5 ppm) and toluene sulfonates (LC-MS; 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 colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains FD&C yellow #6/sunset yellow FCF aluminium lake, hypromellose, macrogol/PEG, polysorbate 80 and titanium dioxide. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an orange, modified capsule shaped, biconvex, film coated tablet, debossed with 'H' on one side and 'A1' on other side. The tablets are packaged in an HDPE bottle with child resistant cap containing a canister with 2 gram silica gel desiccant and in Al-Al blisters.

The objective was to develop a stable, fixed-dose combination, essentially similar in formulation and bioequivalent to the WHO comparator product, Epzicom®. The comparator product was characterized for composition, physicochemical characteristics and in vitro dissolution profiles to define a quality target product profile. The excipients selected are the same as those of the comparator product with the addition of colloidal silicon dioxide included as glidant. Compatibility studies done on binary mixtures showed that the APIs are compatible with each other and the excipients.

Using different granulation techniques, various trial batches were produced and analysed for physicochemical characteristics and dissolution profiles. Finally the individual aqueous wet granulation of abacavir sulfate and lamivudine was selected as manufacturing process. Optimization studies were performed to establish the concentration of disintegrant, diluent, glidant and lubricant. 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) and colorants, average weight, water content (KF), dissolution (HPLC), uniformity of dosage units (by content uniformity), related compounds (HPLC), assay (HPLC) and microbial limits. The

test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with very little degradation. 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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of [HA657 trade name] of Hetero Labs Limited, India comparing with that of Epzicom® (abacavir sulfate and lamivudine) 600/300 mg tablets of ViiV Healthcare Research Triangle Park, NC 27709 in normal, healthy, adult, human subjects under fasting conditions (study no. 555-12).

The objective of the study was to compare the bioavailability of the stated Abacavir sulfate/Lamivudine 600/300mg FDC tablet manufactured by/for Hetero Labs Limited, India (test drug) with the reference formulation Epzicom® (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 two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Abacavir sulfate/Lamivudine 600/300mg (abacavir sulfate 600 mg + lamivudine 300 mg) Batch no. ABL212001.
Treatment R:	Reference – 1 tablet Epzicom® (abacavir sulfate 600 mg + lamivudine 300 mg) Batch no. 1ZP3132.

A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 abacavir and lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/ml for abacavir and 25 ng/ml for lamivudine.

The study was performed with 38 participants; data generated from a total of 38 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) #	1.50 (0.75 – 4.0)	1.50 (0.25 – 3.0)	-	-
C_{max} (ng/ml)	5723 ± 1396 (5572)	6115 ± 1871 (5874)	94.9	89.8 – 100.2
AUC_{0-t} (ng.h/ml)	17806 ± 4297 (17332)	17761 ± 3907 (17344)	99.9	97.2 – 102.8
AUC_{0-inf} (ng.h/ml)	17960 ± 4324 (17484)	17905 ± 3934 (17485)	100.0	97.2 – 102.8

* geometric mean; # median (range)

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) #	2.25 (0.75 – 5.0)	2.0 (0.75 – 6.0)	-	-
C_{max} (ng/ml)	2608 ± 732 (2507)	2670 ± 722 (2561)	97.9	92.5 – 103.6
AUC_{0-t} (ng.h/ml)	14605 ± 3320 (14255)	14826 ± 3468 (14387)	99.1	95.4 – 102.9
AUC_{0-inf} (ng.h/ml)	14864 ± 3311 (14522)	15091 ± 3484 (14658)	99.1	95.5 – 102.8

* geometric mean; # median (range)

Conclusion

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 FDC tablet [HA657 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the comparator product Epzicom® (ViiV Healthcare).

4. Summary of product safety and efficacy

[HA657 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 [HA657 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 to be acceptable when guidance and restrictions stated in the summary of product characteristics are considered. 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 [HA657 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA657 trade name] has shown to be bioequivalent with Epzicom® (ViiV Healthcare, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA657 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [HA657 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 has advised that the quality, efficacy and safety of [HA657 trade name] allow inclusion of [HA657 trade name], manufactured at Hetero Labs Limited, Unit – V, Sy No. 439, 440, 441 & 458,TSIIC Formulation SEZ, Polepally (V),Jadcherla (M), Mahaboobnagar District, Telangana, India in the list of prequalified medicinal products.