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	[HA518 trade name]*
Manufacturer of Prequalified Product	Cipla Ltd, Manufacturing Division Plot No. A – 33/1/2 Patalganga Industrial Area, District – Raigad 410220 Patalganga Maharashtra India
Active Pharmaceutical Ingredients (APIs)	Abacavir (as sulfate)/lamivudine
International Nonproprietary Name	Abacavir/lamivudine
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors, (J05AR02)
Therapeutic indication	[HA518 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.

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

1. Introduction

[HA518 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. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA518 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 Ingredients (APIs)

Abacavir sulfate

Based on scientific principles, the WHO PQP has identified abacavir (as sulfate) (up to 600mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble.

The manufacture of abacavir sulfate, which contains two chiral carbon atoms, entails several chemical steps. The desired stereochemistry at the chiral centres is built into the starting material. The reactions involved in the conversion of the starting material to the API do not involve the chiral centres and hence the original chirality of the starting material is preserved and retained in the final API. The critical process parameters were defined in the synthesis of abacavir sulfate and they are routinely monitored.

The API specifications are pharmacopoeial based and include tests for description, identification (IR, HPLC and counter ion), assay, residue on ignition, related compounds (HPLC), enantiomeric purity (chiral HPLC; enantiomer $\leq 0.30\%$), water content, solubility, specific optical rotation, heavy metals, content of sulfate 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 packing material.

Lamivudine

Based on scientific principles the WHO PQP has identified lamivudine (up to 300mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus highly soluble over the pH range 1 to 6.8.

Lamivudine is described in the Ph.Int., Ph.Eur. and the USP, and is considered well-established in the WHO PQP.

The specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), light absorption, water content, limit of lamivudine enantiomer (chiral HPLC; $\leq 0.3\%$), chromatographic purity (HPLC), assay, polymorphic form (XRPD), residue on ignition, heavy metals, melting range, specific optical rotation, particle size, tapped density 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 dispersible tablet formulation include microcrystalline cellulose, sodium starch glycolate, hypromellose, corn starch, strawberry cream flavour, aspartame, colloidal silicon dioxide and magnesium stearate. A TSE/BSE free declaration has been provided for each excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA518 trade name] are white to off white capsule shaped, biconvex, uncoated tablets with central break-line on one side and 'C' debossed on other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in an HDPE bottle with HDPE screw cap, also containing a 1 g silica gel bag and rayon sanicoil.

The development of the composition of the dispersible tablets, targeted towards the paediatric population, has been described. The excipients used in the formulation design were selected from prior knowledge and variability with respect to their physicochemical and functional properties and the qualitative composition of the comparator product (Epzicom® tablets, containing 600 mg of abacavir (as sulfate) and 300 mg of lamivudine), supported by excipient compatibility studies. Aspartame and strawberry cream flavour have been included to render the formulation acceptable and palatable for the paediatric population.

Wet granulation was considered to be the process of choice as it achieves better content uniformity and compressibility, compared to direct compression. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three primary batches demonstrated the consistency of the process.

Product specification

The proposed specifications are regarded adequate for ensuring consistent quality of this FPP and include tests for description, identification (HPLC and TLC), average weigh, hardness, friability, disintegration (≤ 3 minutes), fineness of dispersion, water content, uniformity of dosage units (by content uniformity), dissolution, degradation products (HPLC), assay (HPLC)and microbiological examination of non-sterile products.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/65%RH as long-term storage conditions and at accelerated conditions. The results were well within the agreed specifications at all storage conditions and a shelf-life of 24 months has been allowed for the FPP when stored not above 30°C.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2009 according to internationally accepted guidelines:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of ten fixed dose combination pediatric tablets of Abacavir 60 mg and Lamivudine 30 mg of Cipla Limited, India with EPZICOM® (containing 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine) tablets of GlaxoSmithKline, USA in 28 healthy human adult subjects, under fasting conditions. (study no. 125-09).

The objective of the study was to compare the bioavailability of the stated Abacavir/Lamivudine 60mg/30 mg fixed dose combination tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Epzicom®, GSK) and to assess bioequivalence. The comparison was

performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 10 tablets Abacavir/Lamivudine 60mg/30 mg (abacavir 600 mg + lamivudine 300 mg) Batch no. K80730.
Treatment R: Reference – 1 tablet Epzicom® (abacavir 600 mg + lamivudine 300 mg) Batch no. R412340.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 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 99 ng/ml for abacavir and 80 ng/ml for lamivudine.

The study was performed with 28 participants; data generated from a total of 25 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)	0.80 ± 0.59	1.33 ± 0.67	-	-
C_{max} (ng/ml)	5838 ± 2023 (5588)	5459 ± 1332 (5299)	105.7	95.6 – 116.8
AUC_{0-t} (ng.h/ml)	15059 ± 2456 (14888)	14704 ± 2224 (14540)	102.5	98.9 – 106.2
AUC_{0-inf} (ng.h/ml)	15374 ± 2460 (15204)	15020 ± 2236 (14858)	102.4	98.8 – 106.2

* 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)	1.86 ± 0.84	2.30 ± 0.81	-	-
C_{max} (ng/ml)	2868 ± 689 (2789)	2876 ± 856 (2739)	102.0	94.2 – 110.3
AUC_{0-t} (ng.h/ml)	14280 ± 3297 (13898)	14241 ± 4561 (13417)	103.6	95.2 – 112.6
AUC_{0-inf} (ng.h/ml)	14779 ± 3357 (14402)	14796 ± 4602 (14007)	102.8	95.1 – 111.1

* geometric mean

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 fixed dose combination tablet Abacavir/Lamivudine 60mg/30 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Epzicom® (GSK).

4. Summary of product safety and efficacy

[HA518 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Epzicom® for which benefits have been proven in terms of virological and immunological efficacy, taking into account the difference in strengths.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. 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 [HA518 trade name] is used in accordance with the SmPC.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA518 trade name] has shown to be bioequivalent with Epzicom® tablets (GlaxoSmithKline, USA), taking into account the difference in strengths.

Efficacy and Safety

Regarding clinical efficacy and safety [HA518 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [HA518 trade name] was acceptable for the following indication: **"Antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in children weighing at least 3 to 25 kg."** and has advised to include [HA518 trade name], manufactured at Cipla Ltd, Manufacturing Division Plot No. A – 33/1/2, Patalganga Industrial Area, District – Raigad, 410220 Patalganga, Maharashtra,India in the list of prequalified medicinal products.