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	[HA662 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited Plot No A – 33, A – 2 (Unit – I) MIDC Patalganga District Raigad, 410 220 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Abacavir (as sulfate)/Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, ATC code: J05AR02.
Therapeutic indication	[HA662 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children

1. Introduction

[HA662 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

[HA662 trade name] should be prescribed by a healthcare 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 600mg oral dose) as a BCS class 3 API. The API is thus highly soluble over the pH range 1 to 6.8.

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.

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

The API specifications are pharmacopoeial based and include tests for description, identification (IR, HPLC and counter ion), assay (HPLC), residue on ignition, related compounds (HPLC), enantiomeric purity (chiral HPLC; enantiomer ≤ 0.30%), water content (KF), solubility, specific optical rotation, heavy metals, polymorphic identity (XRPD), content of sulfate, mesityl oxide (GC-MS; ≤ 2.5 ppm) 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 PQTm has identified lamivudine (up to 300mg oral dose) as a BCS class 3 API. 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 PQTm.

The specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), assay (HPLC), limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), other related compounds (HPLC), water content (KF), light absorption, polymorphic identity (XRPD), residue on ignition, heavy metals, melting range, specific optical rotation, 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. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA662 trade name] are white to off white, capsule shaped, biconvex, uncoated tablets debossed with “CJ” on one side and deep score-line on the other side. The score-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 CRC polypropylene cap, also containing a 1 g silica gel bag and rayon sanicoil.

Two strengths of Abacavir (as sulfate)/Lamivudine Dispersible Tablets, proportionally similar in composition, were developed: 60mg/30mg and 120mg/60mg. The development focused on the lower strength, which has been prequalified first.

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 WHO 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 achieved better content uniformity and compressibility, compared to direct compression. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. The two strengths showed very rapidly dissolution properties in the main BCS media, supporting an additional strength biowaiver for the higher strength

Specifications

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

Stability testing

Stability studies have been conducted at 30 C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided show that the product is quite stable with little degradation. No significant change was observed at accelerated conditions. Photo stability results revealed that the product is photo stable. 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 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 ten fixed dose combination tablets 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 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**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

Lamivudine

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)	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

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax 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

[HA662 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, [HA662 trade name] is pharmaceutically and

therapeutically equivalent and thus interchangeable with the comparator product Epzicom® for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA662 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 [HA662 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA662 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA662 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 [HA662 trade name] was acceptable for the following indication: **"in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children"**, and would allow inclusion of [HA662 trade name], manufactured at Cipla Limited, Plot No A – 33, A – 2 (Unit – I), MIDC Patalganga, District Raigad, 410 220 , Maharashtra, India in the list of prequalified medicinal products.