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

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|---|---|
| **Name of the Finished Pharmaceutical Product** | [HA743 trade name][*] |
| **Manufacturer of Prequalified Product** | Cipla Limited<br>Unit 2, Plot No A – 42<br>MIDC Industrial Area<br>Patalganga<br>District Raigad<br>Maharashtra 410 220<br>India.<br><br>Cipla Limited<br>Unit 7, Plot No. S- 103 to S- 105,<br>S-107 to S-112, L-147<br>L-147/1 to L-147/3<br>L-147/A & L-138<br>Verna Industrial Estate<br>Salcette<br>Goa – 403 722<br>India. |
| **Active Pharmaceutical Ingredient(s) (API)** | Abacavir (as sulfate) and lamivudine |
| **Pharmaco-therapeutic group (ATC Code)** | Antivirals for treatment of HIV infections, combinations (J05AR02) |
| **Therapeutic indication** | [HA743 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

[HA743 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.

It is recommended that therapy therapy should be prescribed 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*

Abacavir sulfate has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [HA743 trade name], is of good quality and manufactured in

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

accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

*Lamivudine*

Based on scientific principles WHO PQTm has provisionally identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus considered BCS highly soluble over the pH range 1 to 6.8. 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 range, identification (IR and HPLC), assay (HPLC), limit of lamivudine enantiomer (HPLC; ≤ 0.30%), related substances (HPLC), water determination, light absorption, polymorphic identity, residue on ignition, heavy metals, specific optical rotation, tapped density and residual solvents (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.

**Other ingredients**

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate, hypromellose, corn starch, colloidal silicon dioxide and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, FD&C yellow #6/sunset yellow FCF aluminium lake, macrogol/ polyethylene glycol and polysorbate 80.

The excipients are supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regard to all the excipients. None of the excipients are derived from human or animal sources.

**Finished pharmaceutical product (FPP)**

*Pharmaceutical development and manufacture*

The multisource product is an orange coloured, capsule shaped, biconvex, film coated tablet, debossed with ‘C’ on one side and plain on the other side. The tablets are packaged in a white HDPE container with 1g silica gel bag containing 30 tablets. The closures are either white non-child resistant HDPE, white polypropylene child resistant or blue polypropylene child resistant caps.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator product, Epzicom ™ (abacavir (as sulfate)/lamivudine 600 mg/ 300 mg) tablets. The excipients used in the formulation design were selected from prior knowledge and with respect to their physicochemical and functional properties and the qualitative composition of the comparator product, supported by excipient compatibility studies. Wet granulation was chosen as the manufacturing 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. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

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 identification of the API (HPLC and TLC), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), organic impurities (HPLC), description, average weight, water content, residual solvents (GC) and

microbiological examination of non-sterile products. The test methods have been satisfactorily described and validated.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH 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 data showed all the parameters met their acceptance criteria at both long-term and accelerated storage conditions, with no apparent negative trend, in the proposed packaging configuration. 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 2009/2010 according to internationally accepted guidelines:

Bioequivalence study comparing fixed dose combination of Abacavir 600 mg as Abacavir sulfate and Lamivudine 300 mg tablet of Cipla Ltd., India with EPZICOM™ tablet (containing abacavir 600 mg as abacavir sulfate and lamivudine 300 mg) of GlaxoSmithKline, USA in healthy adult human subjects under fasting conditions (study no. 09-09-337).

The objective of the study was to compare the bioavailability of the stated Abacavir/Lamivudine 600 mg/300 mg FDC tablet manufactured by Cipla Ltd., India (test drug) with the reference formulation Epzicom™ (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 two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Abacavir/Lamivudine 600 mg/300 mg
(abacavir 600 mg + lamivudine 300 mg)
Batch no. K91462.

Treatment R: Reference – 1 tablet Epzicom™
(abacavir 600 mg + lamivudine 300 mg)
Batch no. R426192.

A 11 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 100 ng/mL for abacavir and 50 ng/mL for lamivudine.

The study was performed with 36 participants; data generated from a total of 34 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) | 1.82 ± 0.58 | 1.80 ± 0.61 | – | – |
| $C_{max}$ (ng/mL) | 6190 ± 1328 (6045) | 6335 ± 1170 (6229) | 97.1 | 91.4 – 103.0 |
| $AUC_{0-t}$ (ng·h/mL) | 19210 ± 4353 (18757) | 19121 ± 3922 (18737) | 100.1 | 97.0 – 103.3 |
| $AUC_{0-inf}$ (ng·h/mL) | 19293 ± 4387 (18836) | 19214 ± 3920 (18832) | 100.0 | 97.0 – 103.2 |

**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) | 2.62 ± 0.74 | 2.50 ± 0.81 | – | – |
| $C_{max}$ (ng/mL) | 3021 ± 827 (2903) | 2944 ± 651 (2867) | 101.3 | 94.7-108.2 |
| $AUC_{0-t}$ (ng·h/mL) | 16263 ± 3907 (15764) | 15676 ± 3465 (15283) | 103.2 | 97.1-109.6 |
| $AUC_{0-inf}$ (ng·h/mL) | 16439 ± 3932 (15939) | 15861 ± 3490 (15467) | 103.1 | 97.0-109.5 |

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/Lamivudine 600 mg/300mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Epzicom™ (GlaxoSmithKline).

## 4. Summary of product safety and efficacy

[HA743 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, [HA743 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epzicom™ (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA743 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 [H743 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HA743 trade name] has been shown to be bioequivalent with Epzicom™ (GlaxoSmithKline).

**Efficacy and Safety**

Regarding clinical efficacy and safety, [HA743 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 [HA743 trade name] was acceptable for the following indication: 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, and would allow inclusion of [HA743 trade name], manufactured at Cipla Limited, Unit 2, Plot No A – 42, MIDC Industrial Area, Patalganga, District Raigad, Maharashtra 410 220 and Unit 7, Plot No. S- 103 to S- 105, S-107 to S-112, L-147, L-147/1 to L-147/3, L-147/A & L-138, Verna Industrial Estate, Salcette, Goa – 403 722, India in the list of prequalified medicinal products.