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	[HA354 trade name][*]
Manufacturer of Prequalified Product	Cipla Ltd 289 JBB Marg Mumbai Central Mumbai 400 008 India Phone: +91 22 23082891, 23095521 Fax: +91 22 23070013, 23070393, 23070385 Email: ciplaexp@cipla.com
Active Pharmaceutical Ingredient(s) (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code J05AF05
Therapeutic indication	[HA354 trade name], is indicated for the treatment of HIV-1 infection in adults, adolescents (aged over 12 years), in combination with other antiretroviral agents.

1. Introduction

[HA354 trade name], is indicated for the treatment of HIV-1 infection in adults and adolescents (aged over 12 years), in combination with other antiretroviral agents.

[HA354 trade name] is not indicated for use in patients with clinically significant hypersensitivity to lamivudine or to any of the components contained in the formulation.

It is recommended that therapy is given only 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)

Lamivudine is a class 1 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms).* It is thus highly soluble in aqueous medium over the pH range 1–6.8.

Lamivudine API is described in the Ph.Int., Ph.Eur. and the USP, and is considered well-established in the Prequalification Programme.

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

The API is adequately controlled by its set of quality specifications which is pharmacopoeial based, with additional in-house specifications including polymorphic identity (Form II), tapped density, particle size 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.

Other ingredients

Other ingredients used in the core tablet formulation include corn starch, magnesium stearate, microcrystalline cellulose and sodium starch glycollate. The film coating contains hydroxypropyl methylcellulose 2910, propylene glycol 6000 (macrogol) and titanium oxide. Assurance by means of a certificate was provided that magnesium stearate is BSE/TSE free.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA354 trade name] are white, capsule-shaped, biconvex film-coated tablets with central break-line on one side and plain on the 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 a cylindrical, white opaque HDPE bottle with continuous thread with a polyethylene screw cap (pack size: 30 or 60 tablets).

The development of the final composition of Lamivudine 300 mg Tablets has been described. The objective was to develop a stable product, essentially similar in composition and bioequivalent to the comparator product, Epivir® 300mg film-coated tablets. The wet granulation method was selected for manufacturing of the core tablets. The multisource product showed dissolution profiles similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three production scale batches demonstrated the consistency of the process.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality of this FPP and include tests for description, identification of the API (HPLC and UV), average weight, uniformity of weight, hardness, disintegration time, dissolution, related substances (HPLC) and assay (HPLC). Batch analysis data confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability testing

Stability studies have been conducted on three primary batches at 30ºC/65%RH as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at both these storage conditions. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2004 according to internationally accepted guidelines.

Randomized, 2-way crossover bioequivalence study of Lamivudine 300 mg tablets & Epivir® administered as 1 x 300 mg tablet in healthy subjects under fasting conditions (study no. 30360).

The objective of the study was to compare the bioavailability of the stated Lamivudine 300 mg tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Epivir®, GlaxoSmithKline) and to assess bioequivalence. The comparison was performed as a

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

Treatment T: Test – 1 tablet Lamivudine 300 mg
(lamivudine 300 mg)
Batch no. G44121.

Treatment R: Reference – 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. B108445.

A 7-day washout period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 17 samples within 24 hours after dosing) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for lamivudine were analysed using a validated HPLC method with UV detection. The limit of quantification was stated to be about 10 ng/ml for lamivudine.

The study was performed with 26 participants; data generated from a total of 26 subjects were used for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine as well as statistical results are summarised below:

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)	1.28 ± 0.58	1.04 ± 0.58	-	-
C_{max} (ng/mL)	2543 ± 822 (2399)	2614 ± 693 (2516)	95.4	88.7–102.6
AUC_{0-t} (ng·h/mL)	10210 ± 2335 (9951)	10356 ± 2306 (10111)	98.4	93.5–103.6
AUC_{0-inf} (ng·h/mL)	10477 ± 2246 (10252)	10607 ± 2301 (10369)	98.9	94.5–103.4

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and Cmax values regarding lamivudine. Accordingly, the test tablet [HA354 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Epivir® (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA354 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, [HA354 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epivir® 300 mg tablets (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [<PQ number> 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 [HA354 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA354 trade name] has been shown to be bioequivalent with Epivir® tablets (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA354 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 [HA354 trade name] was acceptable for the following indication: ' treatment of HIV-1 infection in adults and adolescents (aged over 12 years), in combination with other antiretroviral agents', and would allow inclusion of [HA354 trade name], manufactured at Cipla Ltd, Unit III, IV, VII, Verna Industrial Estate, Verna Salcete, 403 722 Goa, India in the list of prequalified medicinal products.