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	[HA448 trade name]*
Manufacturer of Prequalified Product	Hetero Labs Limited Unit-III, 22-110 Industrial Development Area, Jeedimetla Qutubullapur Municipality Rangareddy District, Hyderabad Zip Code: 500 055 Andhra Pradesh India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine/tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (lamivudine: J05AF05; tenofovir: J05AF07).
Therapeutic indication	[HA448 trade name] tablets is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults and adolescents over 12 years of age.

1. Introduction

[HA448 trade name] is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults and adolescents over 12 years of age.

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)

Lamivudine

Lamivudine is 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 over the pH range 1 to 6.8.

Lamivudine, which is described in the Ph.Int., Ph.Eur. and the USP, is considered well-established in the Prequalification Programme. The specifications are pharmacopoeial based and include tests for description, solubility, identification, light absorbance, melting range, water, limit of lamivudine

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

enantiomer (chiral HPLC), chromatographic purity (HPLC), assay (HPLC), heavy metals, residue on ignition, residual solvents, particle size, bulk and tapped density and specific optical rotation.

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.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is the salt of tenofovir disoproxil with fumaric acid. Tenofovir disoproxil is a diester pro-drug of the purine based nucleotide analogue, tenofovir. The pro-drug has increased oral bioavailability compared to tenofovir disoproxil. Tenofovir disoproxil fumarate is a BCS Class 3 API, i.e. of high solubility and low permeability.

Tenofovir disoproxil fumarate is manufactured in three chemical steps from adenine via (R)-9-(2-hydroxypropyl) adenine. The specifications and test methods for the isolated intermediates are considered to be satisfactory. The structure and stereochemistry of Tenofovir disoproxil fumarate were confirmed by the route of synthesis, and spectrometric data.

The specifications for Tenofovir disoproxil fumarate include description, solubility, clarity of solution, identification of Tenofovir disoproxil fumarate and fumaric acid, melting range, assay and fumaric acid content (HPLC), related substances (HPLC), enantiomeric purity, chloromethyl isopropyl carbonate (GC), 9-propenyladenine, heavy metals, residue on ignition, water content and residual solvents. The limits of the related substances are in agreement ICH Q3A(R2) requirements. The enantiomeric purity, with the limit of the S-enantiomer set at ≤ 1.0%, is controlled by chiral HPLC. The mutagenic 9-propenyladenine, which is a synthesis related substance, is controlled by means of LC-MS at ≤ 5.0 ppm. Tenofovir disoproxil fumarate is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-1140C) and a high melting form (m.p. 114-1180C). Matrix consistently produces high melting form. The test methods have been adequately validated.

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 include colloidal anhydrous silica, croscarmellose sodium, crospovidone, FD&C blue #2/indigo carmine, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose and povidone. Assurance by means of certificates was provided that all excipients are BSE/TSE free.

Finished pharmaceutical product (FPP)

Each tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

[HA448 trade name] are capsule shaped biconvex uncoated tablets, having a blue layer debossed with ‘129’ and a white layer debossed with ‘H’. The tablets are packaged in a white round HDPE bottle containing absorbent cotton and a canister of silica gel, sealed with aluminium foil and fitted with a continuous thread plastic closure.

Pharmaceutical development and manufacture

The development of the final composition of [HA448 trade name] has been described. The objective was to develop a stable fixed-dose combination tablet, bioequivalent to the comparator products, Viread® 245 mg film-coated tablets (containing 300 mg Tenofovir disoproxil fumarate) and Epivir® 300 mg film-coated tablets taken concomitantly. The product has been developed as immediate release solid dosage form for oral administration. The innovator products were characterized for their chemical and physical properties – in particular the dissolution profiles in multimedia were studied and used to select suitable formulations. API-API and API-excipient compatibility have been demonstrated.

The product was developed as a bilayered tablet for aesthetical reasons. The layers have the same composition except for the colorant in the blue layer. Due to the poor flow properties of the APIs direct compression was not considered and a non-aqueous wet granulation process was selected. The manufacturing process was optimized to obtain tablets of desired characteristics, with dissolution profiles similar to that of the innovator products. Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data presented on three production batches demonstrate the consistency of the process and the quality of the product.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality for this FPP and include tests for description, identification of APIs (HPLC and TLC) and colorant, average weight, uniformity of dosage units, water content (Karl Fischer), dissolution (HPLC detection), related compounds, assay and fumaric acid content by HPLC, residual solvent and microbial examination. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been performed on three batches at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The data showed a slight increase for a hydrolysis degradation product. 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 2008 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study of combined Tenofovir disoproxil fumarate 300 mg and Lamivudine 300 mg tablets of Hetero Drugs Ltd, India and individual Viread® (tenofovir disoproxil fumarate) tablets, 300 mg of Gilead sciences, Inc., Foster city, CA 94404, USA and Epivir® (lamivudine) tablet 300 mg of GlaxoSmithKline, Research Triangle Park,NC 27709 in healthy, adult, human subjects under fasting conditions (study no. 07-VIN-204).

The objective of the study was to compare the bioavailability of the stated [HA448 trade name] manufactured by Hetero Drugs Ltd, India (test drug) with the same dose of the individual reference formulations (Viread® 300 mg tablet, Gilead Sciences Inc. and Epivir® 300 mg tablet, 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 – [HA448 trade name] (tenofovir disoproxil fumarate 300 mg + lamivudine 300 mg) Batch no. E8001
Treatment R:	References – Viread® 300 mg tablet (tenofovir disoproxil fumarate 300 mg) Batch no. C6D0288A. – Epivir® 300 mg tablet (lamivudine 300 mg) Batch no. R254058.

A 12 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72 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 tenofovir and lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 3 ng/mL for tenofovir and 60 ng/mL for lamivudine.

The study was performed with 48 participants; data generated from a total of 45 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for tenofovir and lamivudine as well as statistical results are summarised in the following tables:

Tenofovir

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)	1.1 ± 0.5	0.9 ± 0.4	-	-
C_{max} (ng/mL)	297 ± 76 (286)	304 ± 75 (293)	97.4	91.8 – 103.4
AUC_{0-t} (ng·h/mL)	2432 ± 561 (2366)	2376 ± 606 (2302)	102.8	97.7 – 108.2
AUC_{0-inf} (ng·h/mL)	2572 ± 573 (2507)	2526 ± 634 (2448)	102.4	97.6 – 107.5

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)	1.5 ± 0.7	1.4 ± 0.7	-	-
C_{max} (ng/mL)	2525 ± 712 (2414)	2660 ± 803 (2541)	95.0	89.4 – 101.0
AUC_{0-t} (ng·h/mL)	12073 ± 2589 (11800)	12107 ± 2432 (11816)	99.9	95.6 – 104.2
AUC_{0-inf} (ng·h/mL)	12490 ± 2607 (12225)	12529 ± 2462 (12241)	99.9	95.8 – 104.2

The results of the study show that preset acceptance limits of 80 -125 % are met for both AUC and Cmax values regarding tenofovir and lamivudine. Accordingly, the test [HA448 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Viread® 300 mg tablet (Gilead Sciences Inc.) and Epivir® 300 mg tablet (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA448 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, [HA448 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Viread® 300 mg tablets (Gilead sciences, USA) and Epivir® 300 mg tablets (GlaxoSmithKline, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA448 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 [HA448 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA448 trade name] has been shown to be bioequivalent with Viread® 300 mg tablets (Gilead Sciences, USA) and Epivir® 300 mg tablets (GlaxoSmithKline, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA448 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 [HA448 trade name] was acceptable for the following indication: 'in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults and adolescents over 12 years of age', and would allow inclusion of [HA448 trade name], manufactured at Hetero Labs Limited, Unit-III, 22-110, Industrial Development Area, Jeedimetla, Qutubullapur Municipality, Rangareddy District, Hyderabad – 500055, Andhra Pradesh, India, in the list of prequalified medicinal products.