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	[HA666 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited Plot No A – 42 (Unit – II) MIDC Patalganga District Raigad, 410 220 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine + Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	J05AR12
Therapeutic indication	[HA666 trade name] is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected patients weighing 30 kg or more.

1. Introduction

[HA666 trade name] is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected patients weighing 30 kg or more.

[HA666 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 Ingredient (API)

Lamivudine

Based on scientific principles the WHO Prequalification Team – Medicines has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus highly soluble in aqueous medium over the pH range 1.0 – 6.8.

Lamivudine API is described in the Ph.Int., Ph.Eur. and 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 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, residual solvents (GC), alkyl p-toluene sulfonates (≤ 5ppm each) and alkyl methane sulfonates (≤ 5ppm each).

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 (TDF) 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.

TDF, (R)-9-(2-phosphonomethoxypropyl)adenine disoproxil fumarate, is manufactured in several 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 TDF were confirmed by the route of synthesis and spectrometric data. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-1140 C) and a high melting form (m.p. 114-1180 C). The high melting form, controlled by XRPD and melting point, is consistently produced.

The specifications for TDF include tests for description, solubility, identification (IR, HPLC), clarity and colour of solution, water content (KF), fumaric acid content (HPLC), heavy metals, assay (HPLC), 9-propenyladenine (HPLC; ≤ 5 ppm), polymorphic identity (DSC, XRPD), residual solvents (GC), particle size, enantiomeric purity (chiral HPLC; S-isomer ≤ 1.0%) and related substances (HPLC, 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 packaging.

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 core tablet formulation include microcrystalline cellulose, croscarmellose sodium, partially pregelatinised starch and magnesium stearate. The film-coat contains hypromellose, polyvinyl alcohol, titanium dioxide, talc, macrogol/PEG and lecithin (soya). None of the excipients are derived from animal origin. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

The multisource product is a white to off white coloured, capsule shaped, biconvex, film-coated tablet with “LT” debossed on one side and plain on the other side. The tablets are packaged in HDPE bottles also containing 3 silica gel bags, in 3-ply Al-Al blisters or in PVC/ACLAR-Al blisters. The primary packaging provides the necessary protection for the moisture sensitive TDF.

The objective of the development programme was to obtain a stable, immediate release FDC tablet that is bioequivalent to the WHO comparator products Viread® 245mg film-coated tablets (containing 300mg TDF) and Epivir® 300mg film-coated tablets, taken concomitantly. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information on the qualitative composition of the comparator products and compatibility with the APIs. TDF is known to be sensitive to hydrolytic degradation, thus wet granulation was considered impractical. Due to the poor flow properties of the APIs the dry granulation process by roller compaction was selected for manufacture of the core tablets. Optimization studies were performed to meet the desired tablet

characteristics. The tablets showed very rapidly dissolution properties, similar to the comparator products.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the APIs (HPLC, TLC) and the colorant, average weight, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection), degradation products (HPLC), assay (HPLC), residual solvents 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 conditions and for six months at accelerated conditions (40°C/75%RH) in the packaging proposed for marketing of the product. The data showed slight degradation for TDF, though all parameters were well within the agreed limits in all packaging configurations. No significant change was observed at accelerated conditions. 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 2015 according to internationally accepted guidelines.

A randomised, single dose, open label, two-period, cross-over bioequivalence study comparing the test product, Tenofovir disoproxil 245 mg (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir disoproxil fumarate) and Lamivudine 300 mg combination film-coated tablet (Cipla Ltd., India) with the reference products, Viread 245 mg film-coated tablet (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir disoproxil fumarate) of Gilead Sciences International Limited, UK and Epivir® 300 mg film-coated tablet (ViiV Healthcare UK Limited, UK) in healthy adult human subjects under fed conditions (study no. 15-03-040).

The objective of the study was to compare the bioavailability of the stated Tenofovir disoproxil/Lamivudine 245/300mg FDC tablet manufactured by/for Cipla Ltd., India (test drug) with the reference formulations Viread® (Gilead Sciences) and Epivir® (ViiV Healthcare UK Limited) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Tenofovir disoproxil/Lamivudine 245/300mg

(tenofovir disoproxil 245 mg + lamivudine 300 mg) Batch no. PB50740.

Treatment R: References – 1 tablet Viread® (tenofovir disoproxil 245 mg) Batch no. A234358D –

1 tablet Epivir® (lamivudine 300 mg) Batch no. UL0819.

A 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 60 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 9.9 ng/ml for tenofovir and 20 ng/ml for

lamivudine. The study was performed with 32 participants; data generated from a total of 30 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine and tenofovir 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)	2.49 ± 0.75	2.18 ± 0.82	–	–
C_{max} (ng/mL)	323 ± 97 (309)	315 ± 99 (299)	103.5	93.8 – 114.3
AUC_{0-t} (ng·h/mL)	3233 ± 825 (3124)	3225 ± 887 (3099)	100.8	95.2 – 106.7
AUC_{0-inf} (ng·h/mL)	3620 ± 819	3592 ± 904	–	–

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)	2.54 ± 0.63	2.40 ± 1.19	–	–
C_{max} (ng/mL)	2277 ± 505 (2219)	2475 ± 568 (2411)	92.0	87.2 – 97.1
AUC_{0-t} (ng·h/mL)	12966 ± 2642 (12713)	13267 ± 2445 (13062)	97.3	94.0 – 100.8
AUC_{0-inf} (ng·h/mL)	13223 ± 2695	13497 ± 2484	–	–

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding tenofovir and lamivudine. Accordingly, the test FDC tablet Tenofovir disoproxil/Lamivudine 245/300mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Viread® (Gilead Sciences Inc.) and Epivir® (ViiV Healthcare UK Limited).

4. Summary of product safety and efficacy

[HA666 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, [HA666 trade name] is pharmaceutically and therapeutically equivalent and thus

interchangeable with the comparator products, Epivir® (lamivudine 300 mg) and Viread® (tenofovir disoproxil fumarate 300 mg) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA666 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 [HA666 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA666 trade name] has been shown to be bioequivalent with Epivir® 300 mg tablets (ViiV Healthcare, USA) and Viread® 300 mg tablets (Gilead Sciences, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA666 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 [HA666 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 patients weighing 30 kg or more**', and would allow inclusion of [HA666 trade name], manufactured at Cipla Limited, Plot No A-42 (Unit-II), MIDC Patalganga, District Raigad, 410220, Maharashtra, India, in the list of prequalified medicinal products.