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	[HA620 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited Plot No: S-155 to S-159 & N1 Phase III & Phase IV Verna Industrial Estate Verna, Goa- 403722, India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine + Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	J05AR12
Therapeutic indication	[HA620 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

[HA620 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.

[HA620 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.

The API specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR, HPLC), light absorption, water content (KF), heavy metals, residue on

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

ignition, specific optical rotation, lamivudine enantiomer (chiral HPLC; ≤ 0.30%), chromatographic purity (HPLC), assay (HPLC), residual solvents, bulk density, particle size distribution and alkyl methane sulfonates and alkyl para toluene sulfonates (each ≤ 5 ppm).

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 is a BCS Class 3 API, i.e. of high solubility and low permeability.

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), polymorphic form (XRPD), clarity of solution, water content, heavy metals, residue on ignition, melting point (DSC), related compounds (HPLC), enantiomeric impurity (≤ 0.40%; chiral HPLC), assay (HPLC), fumaric acid content, residual solvents and particle size. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5.0 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int. 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 in the core tablet formulation include croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, partially pregelatinized maize starch and sodium starch glycolate. The commercially sourced proprietary film-coating mixture contains hypromellose, macrogol/PEG, polysorbate and titanium dioxide. TSE / BSE free certificates have been provided for the excipients.

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, debossed with ‘I’ on one side and ‘49’ on other side. The tablets are packaged in round, white opaque HDPE bottles, with white polypropylene child resistant cap with heat induction foil inner seal.

The objective of the development programme was to obtain a stable, immediate-release FDC tablet that is bioequivalent to the WHO comparator products Viread® 245 mg film-coated tablets (containing 300 mg TDF) and Epivir® 300 mg 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. The quality target product profile (QTPP) and critical quality attributes were identified.

Due to poor flow properties of the APIs the wet granulation method was selected for manufacture of the core tablets. Optimization studies were performed to meet the QTPP. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification (HPLC, TLC), average weight, uniformity of weight, tablet dimensions, disintegration time, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbial limits. The test methods have been satisfactorily 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 in the packaging proposed for marketing of the product. The data showed degradation for TDF, though all parameters were well within the agreed limits at both storage 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 2012 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two- sequence, single dose, crossover, bioequivalence study of lamivudine and tenofovir disoproxil fumarate tablets 300 mg/300 mg of Micro Labs Limited, India with Epivir® (lamivudine) tablets 300 mg of ViiV Healthcare, NC27709 and Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc., CA94404 in normal, healthy, adult, human subjects under fasting condition (study no. ARL/12/499).

The objective of the study was to compare the bioavailability of the stated Lamivudine/Tenofovir disoproxil fumarate 300 mg/300 mg FDC tablet manufactured by Micro Labs Ltd., India (test drug) with the individual reference formulations Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences) 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 Lamivudine/tenofovir disoproxil fumarate 300 mg/300 mg (lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. LFAG003.
Treatment R:	References – 1 tablet Epivir® (lamivudine 300 mg) Batch no. 1ZP3133 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. DVSY

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 samples within 96 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for lamivudine and tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for lamivudine and about 5 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 36 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:

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)	1.60 ± 0.55	1.35 ± 0.54	–	–
C_{max} (ng/mL)	2776 ± 786 (2680)	2751 ± 823 (2620)	102.3	93.5 – 1111.9
AUC_{0-t} (ng·h/mL)	12770 ± 3151 (12414)	11724 ± 3261 (11252)	110.3	102.3 – 118.9
AUC_{0-inf} (ng·h/mL)	13389 ± 3182 (13038)	12310 ± 3327 (11841)	110.1	102.3 – 118.5

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)	1.22 ± 0.54	0.91 ± 0.31	–	–
C_{max} (ng/mL)	404 ± 109 (390)	420 ± 98 (408)	95.5	91.3 – 100.0
AUC_{0-t} (ng·h/mL)	2977 ± 758 (2881)	2810 ± 636 (2731)	105.5	99.8 – 111.4
AUC_{0-inf} (ng·h/mL)	3213 ± 757 (3124)	3044 ± 618 (2980)	104.8	100.0 – 109.9

Conclusion

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

4. Summary of product safety and efficacy

[HA620 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, [HA620 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 [HA620 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 [HA620 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA620 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, [HA620 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 [HA620 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 [HA620 trade name], manufactured at Micro Labs Limited, Plot No. S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa-403722, India, in the list of prequalified medicinal products.