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	[HA514 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Unit II, Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210, India
Active Pharmaceutical Ingredients (APIs)	Lamivudine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR12).
Therapeutic indication	[HA514 trade name] is indicated in combination with at least one other antiretroviral for the treatment of HIV-1 infection in adults aged over 18 years

1. Introduction

[HA514 trade name] is indicated in combination with at least one other antiretroviral medicine for the treatment of HIV-1 infection in adults aged over 18 years.

[HA514 trade name] should be prescribed on the advice of a physician 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 of Medicines Programme 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, which are pharmacopoeial based, include tests for description, solubility, identification, light absorption, water content, heavy metals, limit of lamivudine enantiomer (chiral

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

HPLC; ≤ 0.3%), chromatographic purity (HPLC), assay (HPLC), residual solvents, bulk density and particle size.

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 (TDF)

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 high solubility.

TDF 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.

The specifications for TDF include tests for description, solubility, identification of the API, of fumaric acid and of the polymorphic form (XRPD), melting range, water content, heavy metals, residue on ignition, fumaric acid content, related substances (HPLC), assay (HPLC), enantiomeric purity (S-isomer ≤ 0.2%), residual solvents, particle size and bulk density. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int.

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 and magnesium stearate. The commercially sourced proprietary film-coating mixture contains lactose monohydrate, hypromellose, titanium dioxide and triacetin. TSE/BSE free certifications have been provided.

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 product is a white to off-white coloured, capsule shaped, biconvex, film-coated tablet debossed 'CL71' on one side of the tablet and having plain surface on the other side. The tablets are presented in an HDPE bottle, also containing a silica gel sachet, and in Alu-Alu blisters.

The objective of the development programme was to obtain a stable, robust, 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. Due to the poor flow properties of TDF direct compression was not considered. Compatibility studies indicated an increase in TDF impurities in presence of water due to hydrolytic degradation. A non-aqueous solvent was therefore selected for granulation. Optimum levels of the functional excipients in the formulation ensured dissolution profiles similar to those of the comparator products and acceptable physical characteristics of the tablets like hardness, friability and uniformity of weight. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorant, average weight, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), residual solvent, microbial enumeration and specified microorganisms. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH and 25°C/60%RH as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Degradation of TDF was observed, less significant at zone II than zone IVb 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 2011 according to internationally accepted guidelines:

Bioequivalence study of single dose of fixed dose combination of lamivudine and tenofovir disoproxil fumarate tablets 300 + 300 mg (each tablet contains 300 mg of lamivudine USP and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with separate formulations of Epivir® (lamivudine) tablets 300 mg (each tablet contains 300 mg of lamivudine) manufactured for GlaxoSmithKline, USA and Viread® (tenofovir disoproxil fumarate) tablets 300 mg (each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil) manufactured for Gilead Sciences, Inc., USA in healthy, adult, human subjects under fasting condition (study no. BEQ-514-LT (F)-2010).

The objective of the study was to compare the bioavailability of the stated lamivudine/tenofovir disoproxil fumarate 300 mg/300 mg fixed dose combination tablet manufactured by Macleods Pharmaceuticals Limited, India (test drug) with the same dose of the individual reference formulations (Epivir®, GlaxoSmithKline, and Viread®, Gilead Sciences Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male 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. ELA6001A.
Treatment R:	References – 1 tablet Epivir® (lamivudine 300 mg) Batch no. OC002. – 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. XBF.

A 9-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 26 samples within 96 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} 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 25 ng/ mL for lamivudine and 5 ng/ mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 32 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 (ANOVA log)
t_{max} (h)	1.44 ± 0.49	1.34 ± 0.56	–	–
C_{max} (ng/mL)	3114 ± 849 (3001)	3135 ± 961 (3024)	99.2	91.8 – 107.3
AUC_{0-t} (ng·h/mL)	14027 ± 3026 (13764)	13409 ± 3821 (12936)	106.4	100.7 – 112.4
AUC_{0-inf} (ng·h/mL)	14337 ± 3026 (14084)	13775 ± 3775 (13329)	105.7	100.2 – 111.4

* geometric mean

Tenofovir

Pharmacokinetic Parameter	**Test formulation** (T) arithmetic mean ± SD (*)	**Reference (R)** arithmetic mean ± SD (*)	**log-transformed parameters**	
			Ratio T/R (%)	Conventional 90% CI (ANOVA log)
tmax (h)	1.07 ± 0.40	1.07 ± 0.46	-	-
Cmax (ng/ mL)	249 ± 73 (239)	254 ± 60 (248)	96.4	89.2 – 104.1
AUC0-t (ng.h/mL)	1795 ± 391 (1756)	1723 ± 451 (1673)	105.0	97.8 – 112.6
AUC0-inf (ng.h/mL)	1986 ± 415 (1946)	2039 ± 944 (1924)	101.2	92.7 – 110.4

* geometric mean

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 fixed dose combination 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® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA514 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, [HA514 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA514 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 [HA514 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA514 trade name] has been shown to be bioequivalent with Epivir® (lamivudine 300 mg) and Viread® (tenofovir disoproxil fumarate 300 mg).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA514 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 [HA514 trade name] was acceptable for the following indication: '**in combination with at least one other antiretroviral medicine for the treatment of HIV-1 infection in adults aged over 18 years**', and would allow inclusion of [HA514 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India, in the list of prequalified medicinal products.