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	[HA414 trade name][*]
Manufacturer of Prequalified Product	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C Sinnar Nashik 422113 Maharashtra 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	Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults over 18 years of age.

1. Introduction

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is indicated in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults over 18 years of age.

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is contraindicated in patients with hypersensitivity to the active substances or to any of the excipients.

It is recommended that therapy is given only on the advice of a physician experienced in the treatment of HIV/AIDS.

2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

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*

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

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 obtained from within the Matrix group of companies, is well known API, described in the Ph.Int., the Ph.Eur. and the USP. The specifications include description, identification (HPLC and TLC), light absorption limit, melting range, water, assay (HPLC), chromatographic purity (HPLC), enatiomeric purity (0.3%; chiral HPLC), heavy metals, residue on ignition, residual solvents, particle size, bulk and tapped density and specific optical rotation.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 60 months was allowed for lamivudine when stored not above 30°C.

Tenofovir disoproxil fumarate

The API is obtained from within the Matrix group of companies and the APIMF has been assessed through WHO's APIMF procedure. 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 disoproxil. TDF is a BCS Class 3 API, i.e. of high solubility and low permeability.

TDF 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 TDF were confirmed by the route of synthesis, and spectrometric data.

The specifications for TDF include description, clarity of solution, identification of TDF and fumaric acid, assay and fumaric acid content by HPLC, related substances by HPLC, heavy metals, residue on ignition, water content, chloro methyl isopropyl carbonate (by GC) and residual solvents. The limits of the related substances are in agreement ICH Q3A(R2) requirements. The enatiomeric purity, with the limit of the S-enatiomer 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. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114^{0}C) and a high melting form (m.p. 114-118^{0}C). Matrix consistently produces high melting form. The test methods have been adequately validated.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 30 months was allowed for the API, when stored at 2ºC – 8ºC under nitrogen in sealed, double antistatic LDPE bags, placed into a triple polylaminated aluminium bag, which is sealed and placed in an HDPE drum.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating contains hypromellose, propylene glycol and titanium dioxide. All the excipients are compendial. TSE/BSE free certification is provided for lactose monohydrate. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet. A TSE certificate of suitability (CEP) has been issued by EDQM for magnesium stearate.

Finished Pharmaceutical Product (FPP)

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

Pharmaceutical development

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets are white to off white coloured, oval shaped, biconvex, film-coated tablets debossed "M112" on one side and plain on the other side. The tablets are packaged in a white opaque HDPE bottle fitted with white opaque child resistant or screw cap and containing a molecular sieve desiccant and rayon (pack size: 30's and 100's).

The development of the final composition of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets has been described. The objective was to develop a stable fixed-dose combination tablet, bioequivalent to the innovator products, Viread® 245mg film-coated tablets (containing 300mg TDF) and Epivir® 300mg film-coated tablets taken concomitantly. The tablets have been developed as immediate release solid dosage forms for oral administration. Comparative dissolution tests against the innovator products in multi BCS media were used to select suitable formulations.

Direct compression was not considered due to the poor flow properties of TDF, whereas wet granulation is disfavoured due to the sensitivity of TDF towards hydrolytic degradation. The process developed entails a dry granulation process for TDF, with lamivudine being introduced extragranularly. Each of the excipients was selected for its intended use based on previous experience, the qualitative composition of the innovator products and optimization studies. In the manufacturing process the materials are sifted, blended, roller compacted, milled/screened, recompacted, milled/screened, blended and compressed. This is followed by film-coating and packing. The critical steps of the manufacturing process were optimized to obtain tablets of desired characteristics, with dissolution profiles similar to that of the innovator products.

Validation data were presented for six batches, three each at the lower and higher end of the proposed production scale range, demonstrated the consistency of the process and the quality of the product. Satisfactory in-process controls have been established.

The finished product specifications are regarded adequate for ensuring consistent quality for this FPP and include tests for description, identification of the API (HPLC and TLC) and titanium dioxide in the film-coating, dissolution (HPLC detection), uniformity of dosage units, related substances, thickness and assay (HPLC), water (Karl Fischer) and microbial purity. The test methods have been satisfactorily described and validated. Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability testing

Stability studies have been performed on the six batches used in the process validation studies at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product, i.e. in both pack sizes. The effect of exposure to light has not been studied. The data showed little change with time and were well within the agreed specifications at both storage conditions. At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored in the original container at a temperature not above 30°C and protected from light.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of combined Tenofovir disoproxil fumarate 300mg and Lamivudine 300mg tablets of Matrix Laboratories Limited (India) and individual Viread® (Tenofovir disoproxil fumarate) 300mg of Gilead Sciences, USA and Epivir® (Lamivudine) 300mg tablets of GlaxoSmithKline, USA in healthy human adult male subjects, under fed conditions (study no. 06-VIN-171).

The objective of the study was to compare the bioavailability of the stated tenofovir disoproxil fumarate/lamivudine 300/300 mg fixed dose combination tablet manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the separate reference formulations (Viread 300 mg tablet, Gilead Sciences, 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 male 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 fumarate/lamivudine 300/300 mg

(tenofovir disoproxil fumarate + lamivudine 300/300 mg dose)
Batch no. TLDA536001.

Treatment R: Reference

– 1 tablet Viread® 300 mg

(tenofovir disoproxil fumarate 300 mg dose)

Batch no. FDB023.

– 1 tablet Epivir® 300 mg

(lamivudine 300 mg dose)

Batch no. R245588.

A 10 day wash-out period was observed between administration of test and references. 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 5 ng/ml for tenofovir and 25 ng/ml for lamivudine.

The study was performed with 38 participants; data generated from a total of 35 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.06 ± 0.61	1.79 ± 0.66	-	-
C_{max} (ng/ml)	312 ± 68 (304)	321 ± 72 (313)	97.0	92.1 – 102.1
AUC_{0-t} (ng.h/ml)	2754 ± 586 (2700)	2707 ± 680 (2629)	102.7	99.6 – 105.9
AUC_{0-inf} (ng.h/ml)	2970 ± 565 (2923)	2940 ± 681 (2867)	102.0	99.0 – 105.1

* geometric mean

Lamivudine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.15 ± 0.87	1.97 ± 0.69	-	-
C_{max} (µg/ml)	2.24 ± 0.69 (2.15)	2.18 ± 0.73 (2.07)	103.7	98.3 – 109.5
AUC_{0-t} (µg.h/ml)	10.54 ± 2.94 (10.17)	10.17 ± 2.95 (9.75)	104.3	100.9 – 107.9
AUC_{0-inf} (µg.h/ml)	10.83 ± 2.94 (10.48)	10.46 ± 2.95 (10.05)	104.3	101.0 – 107.7

* geometric mean

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding tenofovir and lamivudine. Accordingly, the test fixed dose combination tablet Lamivudine/Tenofovir disoproxil fumarate 300mg/300 mg Tablets meets the criteria for bioequivalence

with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Viread® (Gilead Sciences) and Epivir® (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products Viread® and Epivir® for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made to the SPC (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 Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is used in accordance with the conditions as stated in the SPC.

Bioequivalence

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets has shown to be bioequivalent with Viread® (Gilead Sciences, USA) and Epivir® (GlaxoSmithKline, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets was acceptable for the following indication: **"in combination with at least one other antiretroviral medicinal product for the treatment of HIV-1 infected adults over 18 years of age",** and has advised that the quality, efficacy and safety of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets are acceptable to allow inclusion of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets, manufactured at Matrix Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik 422113, Maharashtra, India in the list of prequalified medicinal products.