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	[HA410 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)	Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07).
Therapeutic indication	[HA410 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age. [HA410 trade name] is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

1. Introduction

[HA410 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age.

[HA410 trade name] is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

[HA410 trade name] is contraindicated in patients with hypersensitivity to the active substance 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 or hepatitis B.

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*.

*Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
†Formerly Matrix Laboratories Limited.

Active pharmaceutical Ingredient (API)

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, controlled by DSC. 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 approved 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 FD & C Blue #2/Indigo carmine aluminium lake, hypromellose, lactose monohydrate, titanium dioxide and triacetin/glycerol triacetate. Assurance by means of certificates was provided that all excipients are BSE/TSE free.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

[HA410 trade name] are light blue coloured, round biconvex film-coated tablets debossed with "153" on one side and "M" on other side. The tablets are presented in a white opaque wide mouth HDPE bottle with a white opaque cap and containing a desiccant (pack size: 30's and 100's).

The development of the final composition of [HA410 trade name] has been described. The objective was to develop a stable product, essential similar in formulation and bioequivalent to the innovator product, Viread® film-coated tablets. The tablets have been developed as immediate release solid dosage forms for oral administration. The qualitative formulation was developed and each of the excipient was selected for its intended use based on optimization studies. The dry granulation process was selected as the manufacturing process as this is the simplest and most preferred technique for the tablet manufacturing and involves lesser unit operations. The dry granulation process is also preferred since it limits degradation of the API, which is sensitive towards hydrolysis. 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 as discussed in the product development report.

Validation data presented for three batches (at the lower end of the production range) demonstrated the consistency of the process and the quality of the product. The proposed specifications are regarded adequate for ensuring consistent quality for this finished pharmaceutical product. This is supported by batch analytical data.

Comparative dissolution studies conducted in the three BCS media according to the requirements of WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (TRS937, Annex 7) demonstrated that the biobatch – which was also one of the batches used in stability testing and process validation – of Tenofovir Disoproxil Fumarate 300 mg tablets is similar to the batch of Viread® film-coated tablets used in bioequivalence studies with respect to dissolution profiles.

Stability testing

Stability studies have been performed on the same three 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. The data showed little change with time and were well within the agreed specifications at both storage conditions. Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Conclusion

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, balanced, two treatments, two period, two sequence, single dose, crossover, bioequivalence study of [HA410 trade name] (Matrix Laboratories Ltd, India) with Viread® (Tenofovir disoproxil fumarate) 300 mg tablets, manufactured for Gilead Sciences, Inc. USA, in 32 healthy human adult male subjects under fed conditions (study no. 033-06).

The objective of the study was to compare the bioavailability of the stated tenofovir disoproxil fumarate 300 mg tablets manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the reference formulation (Viread 300 mg tablet, Gilead Sciences) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomised, single dose, crossover study in healthy male subjects under fed conditions. Each subject was assigned to receive one of the following two treatments:

Treatment T:	Test – [HA410 trade name] (tenofovir disoproxil fumarate 300 mg) Batch no. TDFA536001.
Treatment R:	Reference – Viread® 300 mg tablet (tenofovir disoproxil fumarate 300 mg) Batch no. FDB023.

A 10 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 were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/mL for tenofovir.

The study was performed with 32 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 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)	1.89 ± 0.98	1.96 ± 1.03	–	–
C_{max} (ng/mL)	380 ± 145 (356)	395 ± 119 (377)	94.3	87.2 – 101.9
AUC_{0-t} (ng·h/mL)	3295 ± 1050 (3123)	3398 ± 974 (3259)	95.8	90.5 – 101.5
AUC_{0-inf} (ng·h/mL)	3595 ± 1019 (3448)	3668 ± 990 (3644)	94.6	89.0 – 100.7

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. Accordingly, the test tablet of [HA410 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Viread® (Gilead Sciences).

4. Summary of product safety and efficacy

[HA410 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, [HA410 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Viread® (Gilead Sciences, Inc. USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA410 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 [HA410 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA410 trade name] has been shown to be bioequivalent with Viread® (Gilead Sciences, Inc. USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA410 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 [HA410 trade name] was acceptable for the following indications**: 'treatment of HIV-1 infected adults over 18 years of age in combination with other antiretroviral medicinal products" and "treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis'**, and would allow inclusion of [HA410 trade name], 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.