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	[HA417 trade name] *
Manufacturer of Prequalified Product	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C Sinnar 422113 Nashik Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use; Antivirals for treatment of HIV infections, combinations (J05AR03).
Therapeutic indication	[HA417 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age.

1. Introduction

[HA417 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age.

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 Ingredient (API)

Emtricitabine

The API is obtained from within the Matrix group of companies and the APIMF has been assessed through WHO's APIMF procedure.

Emtricitabine or 4-Amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone has two chiral carbon atoms. The desired stereochemistry is built into the intermediate, which is isolated and purified, in the multi-step synthesis process of emtricitabine. The structure and stereochemistry of this intermediate has been critically evaluated for potential isomerism and possible impact on emtricitabine. The absolute stereochemical configuration (2R,5S) of emtricitabine was confirmed by means of a single crystal X-ray diffraction study. The enatiomer of emtricitabine is

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

controlled at level of not more than 0.3% by chiral HPLC chromatography, while its diastereomers are determined by the HPLC related substances test.

Emtricitabine is known to exhibit polymorphism and exists in Forms I, II, III, hydrated forms and an amorphous form. According to XRPD and DSC data Matrix commercially produces consistently Form I. The forms differ sufficiently in melting point to allow control of Form I by its melting point. The crystal structure of Form I is retained during stability testing.

In addition to the above mentioned tests for stereochemical impurities and the polymorphic form, the specifications for emtricitabine include description, solubility, identification, clarity of solution, specific optical rotation, assay, related substances by HPLC, heavy metals, residue on ignition, loss on drying, residual solvents, alkyl methane sulfonates, bulk density and particle size distribution. The limits of the related substances are in agreement ICH Q3A(R2) requirements.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when emtricitabine is stored in the original packing material.

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 and residual solvents, chloro methyl isopropyl carbonate (by GC). The limits of the related substances are in agreement ICH Q3A requirements. The enatiomeric purity, with the limit of the S-enatiomer set at $\leq 1.0\%$, 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.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when TDF is stored in the original packing material at the proposed storage conditions.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. 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. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, triacetin and FD&C Blue#2.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 200mg of emtricitabine and 300mg TDF equivalent to 245mg of tenofovir disoproxil or 136mg of tenofovir.

[HA417 trade name] tablets are blue-coloured, oval-shaped, film-coated tablets debossed with "M117" on one side and plain on the other side. The tablets are presented in a white opaque HDPE bottle fitted with a white opaque cap and containing a desiccant (pack sizes: 30 and 100) and in cold form blister packs consisting of blister foil with heat seal coating on one side and cold form laminate on the other side.

The development of the final composition of [HA417 trade name] has been described. The objective was to develop a stable fixed-dose combination tablet, essentially similar in formulation and bioequivalent to the innovator product, Truvada® film-coated tablets (Gilead Sciences Inc, USA). 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 and emtricitabine. Due to the sensitivity of TDF towards hydrolytic degradation, wet granulation was also not considered. The process developed entails dry granulation, involving several steps of compaction. Studies were performed to optimize the concentration of each excipient and to optimize process parameters to obtain tablets of desired characteristics, with dissolution profiles similar to that of the innovator product.

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

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the API (HPLC and TLC) and of the colorants in the film-coating, dissolution (HPLC detection), uniformity of dosage units, related substances and assay (HPLC), water (Karl Fischer) and microbial limits. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been conducted on the 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 in the packaging proposed for marketing of the product, i.e. in both blisters and bottles. The data showed little change with time and were well within the agreed specifications 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 2007 according to internationally accepted guidelines.

A randomized, open label, two-period, two-treatment, two-sequence single dose crossover bioequivalence study of [HA417 trade name] of Matrix Laboratories Limited (India) with Truvada® tablets of Gilead Sciences Inc, U.S.A, in normal healthy male subjects under fasting condition (study no. US/AHD/07/003).

The objective of the study was to compare the bioavailability of the stated fixed dose combination [HA417 trade name] tablets manufactured by Matrix Laboratories Limited, India (test drug), with the same dose of the reference formulation (Truvada, 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 [HA417 trade name]
(tenofovir disoproxil fumarate/emtricitabine 300mg/200mg)
Batch no. ETFA537002.

Treatment R: Reference – 1 tablet Truvada®
(tenofovir disoproxil fumarate/emtricitabine 300mg/200mg)
Batch no. FDC065.

A 10 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 emtricitabine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/ml for tenofovir and 25 ng/ml for emtricitabine.

The study was performed with 50 participants; data generated from a total of 43 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 emtricitabine 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)	0.96 ± 0.27	0.98 ± 0.31	-	-
C_{max} (ng/ml)	311 ± 87 (299)	300 ± 93 (285)	104.7	95.2 – 115.2
AUC_{0-72h} (ng.h/ml)	1563 ± 572 (1445)	1499 ± 598 (1366)	105.9	93.9 – 119.4

Emtricitabine

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)	1.45 ± 0.59	1.51 ± 0.51	-	-
C_{max} (ng/ml)	1737 ± 425 (1686)	1718 ± 394 (1677)	100.5	94.6 – 106.9
AUC_{0-t} (ng.h/ml)	8123 ± 1541 (7974)	7935 ± 1507 (7794)	102.3	98.7 – 106.1
AUC_{0-inf} (ng.h/ml)	8747 ± 1636 (8590)	8553 ± 1616 (8401)	102.3	98.7 – 105.9

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding tenofovir and emtricitabine. Accordingly, the test tablet [HA417 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Truvada® (Gilead Sciences Inc).

4. Summary of product safety and efficacy

[HA417 trade name] 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 [HA417 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Truvada® 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 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 [HA417 trade name] is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

[HA417 trade name] has shown to be bioequivalent with Truvada® tablets of Gilead Sciences Inc, U.S.A.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA417 trade name] 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 [HA417 trade name] was acceptable for the following indication: **"in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age",** and has advised that the quality, efficacy and safety of [HA417 trade name] are acceptable to allow inclusion of [HA417 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.