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	[HA444 trade name][*]
Manufacturer of Prequalified Product	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422113, Maharashtra state, India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate.
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR06)
Therapeutic indication	[HA444 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 35 kg with virologic suppression to HIV-1 RNA levels of less than 50 copies/mL on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy.

1. Introduction

[HA444 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 35 kg with virologic suppression to HIV-1 RNA levels of less than 50 copies/mL on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy.

[HA444 trade name] should be prescribed by 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)

Efavirenz

Efavirenz is a class 4/2 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). Data provided in the dossier show that efavirenz is practically insoluble in aqueous medium over the pH range 1.2 to 8.0.

Efavirenz is manufactured in a two-step process from a commercially available starting material. Efavirenz can exist in five crystalline forms (Forms I, II, III, IV and V). The crystalline forms were characterised by X-ray powder diffraction and DSC. Form I is consistently produced.

The efavirenz specifications include tests for description, solubility, identification (infrared, HPLC, polymorphic form by DSC), water (KF), specific optical rotation, residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), residual solvents and particle size distribution.

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

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 enantiomer of emtricitabine is 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 (IR and HPLC), specific optical rotation, assay (HPLC), related substances (HPLC), heavy metals, residue on ignition, loss on drying, residual solvents (GC), alkyl methane sulfonates (GC-MS)and particle size. 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, solubility, clarity of solution, identification of TDF and fumaric acid, assay and fumaric acid content by HPLC (HPLC), related substances (HPLC), heavy metals, residue on ignition, water content (KF), clarity of solution, chloromethyl isopropyl carbonate content (GC) and residual solvents (GC). The limits of the related substances are in agreement ICH Q3A requirements. The enantiomeric purity, with the limit of the S-enantiomer 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. 112-1140 C) and a high melting form (m.p. 114-1180 C). Matrix consistently produces high melting form controlled by DSC. 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, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulphate. Assurance by means of certificates was provided that all excipients are BSE/TSE free. The commercially sourced proprietary film-coating mixture contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol (partially hydrolysed), talc and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 600 mg efavirenz, 200 mg of emtricitabine and 300 mg TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

[HA444 trade name] are pink coloured, capsule shaped, film-coated tablets, debossed with “M171” on one side and plain on the other side. The tablets are presented in a white opaque, round HDPE bottle fitted with a white opaque polypropylene screw cap closure, aluminium sealed, and containing a desiccant (canister of molecular sieve) (pack size: 30 tablets).

The development of the final composition of [HA444 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, Atripla® film-coated tablets. The tablets have been developed as an immediate release solid dosage form for oral administration. The qualitative formulation was developed and each excipient was selected for its intended use based on optimization studies. As the formulation comprises of three different APIs with different physicochemical properties a double layered tablet, similar to the innovator tablet, was developed. In order to improve the flow properties and compressibility of blend, it was decided to follow a wet granulation method for the layer containing efavirenz. For the layer containing TDF and emtricitabine direct compression was not considered due to the poor flow properties of the APIs and due to the sensitivity of TDF towards hydrolytic degradation, wet granulation was also not considered. The process developed for the TDF/emtricitabine layer 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, 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 APIs (HPLC and TLC) and of the colorants in the film-coating, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), 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 30^0C/75%RH (zone IVb) as long-term storage condition and for six months at accelerated conditions

in the packaging proposed for marketing of the product. 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 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, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Tenofovir Disoproxil Fumarate 300 mg and Emtricitabine 200 mg and Efavirenz 600 mg tablets of Matrix Laboratories Limited (India) and ATRIPLATM (Tenofovir Disoproxil Fumarate 300 mg and 200 mg Emtricitabine and Efavirenz 600 mg) tablets of Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A. in healthy human adult male subjects, under fasting conditions (study no. 06/VIN/169).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 600/200/300 mg fixed dose combination tablet manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the reference formulation (AtriplaTM, Bristol-Myers Squibb Company/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 Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg (efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) Batch no. 1001254.
Treatment R:	Reference – 1 tablet Atripla™ (efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) Batch no. V0129A002.

A 32 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72 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 emtricitabine and tenofovir disoproxil fumarate (as tenofovir) were analyzed using a validated LC-MS/MS method and efavirenz was analyzed using a validated HPLC-method with UV-detection. The limit of quantification was stated to be about 50 ng/mL for efavirenz, 30 ng/mL for emtricitabine, and 3 ng/mL for tenofovir.

The study was performed with 48 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 efavirenz, emtricitabine and tenofovir as well as statistical results are summarised in the following tables:

Efavirenz

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)	4.68 ± 3.37	4.14 ± 1.31	–	–
C_{max} (µg /mL)	2.19 ± 0.75 (2.07)	2.19 ± 0.78 (2.06)	100.5	91.2 – 110.7
AUC_{0-72h} (µg·h/mL)	54.2 ± 16.6 (51.9)	54.3 ± 17.4 (51.4)	101.0	93.4 – 109.2

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)	1.59 ± 0.69	1.55 ± 0.53	–	–
C_{max} (µg /mL)	2413 ± 537 (2357)	2410 ± 463 (2360)	99.9	94.1 – 106.0
AUC_{0-t} (µg·h/mL)	12477 ± 2037 (12299)	12192 ± 2267 (11973)	102.7	98.7 – 106.9
AUC_{0-inf} (µg·h/mL)	12832 ± 2044 (12658)	12576 ± 2282 (12362)	102.4	98.6 – 106.4

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)	1.11 ± 0.41	1.02 ± 0.39	–	–
C_{max} (µg /mL)	314 ± 86 (301)	358 ± 114 (340)	88.7	81.3 – 96.7
AUC_{0-t} (µg·h/mL)	2377 ± 452 (2326)	2505 ± 649 (2415)	96.3	89.4 – 103.8
AUC_{0-inf} (µg·h/mL)	2531 ± 487 (2478)	2658 ± 690 (2563)	96.7	90.0 – 103.8

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding efavirenz, emtricitabine and tenofovir. Accordingly, the test fixed dose combination tablet Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 600/200/300 mg meets the criteria for

bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Atripla™ tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.).

4. Summary of product safety and efficacy

[HA444 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, [HA444 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Atripla™ tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA444 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 [HA444 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA444 trade name] has been shown to be bioequivalent with Atripla™ tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA444 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 [HA444 trade name] was acceptable for the following indication: 'treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 35 kg with virologic suppression to HIV-1 RNA levels of less than 50 copies/mL on their current combination antiretroviral therapy for more than three months (patients must not have experienced virological failure on any prior antiretroviral therapy)', and would allow inclusion of [HA444 trade name], manufactured at Matrix Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422113, Maharashtra state, India in the list of prequalified medicinal products.