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	[HA466 trade name]*
Manufacturer of Prequalified Product	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422113, Maharashtra state, India Tel: +91 40 2348 004
Active Pharmaceutical Ingredients (APIs)	efavirenz, lamivudine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, Direct acting antivirals (efavirenz: J05AG03; lamivudine: J05AF05; tenofovir disoproxil: J05AF07).
Therapeutic indication	[HA466 trade name] is indicated treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing at least 40 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

[HA466 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing at least 40 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).

[HA466 trade name] should be prescribed by a physician experienced in the management of HIV infection.

2. Assessment of quality

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

Active pharmaceutical Ingredient (API)

Efavirenz

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

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 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, enantiomeric content (0.5%; chiral HPLC) 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.

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 List of Essential Medicines immediate-release, solid oral dosage forms). It is thus highly soluble over the pH range 1 to 6.8.

Lamivudine is a well known API, described in the Ph.Int., the Ph.Eur. and the USP. The specifications include description, solubility, identification (HPLC and TLC), light absorption limit, melting range, water (KF), 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.

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**.**

Tenofovir disoproxil fumarate

The API 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, identification of TDF and fumaric acid, assay and fumaric acid content (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 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 $\leq$ 5.0 ppm. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-1140C) and a high melting form (m.p. 114-1180C). 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, sodium chloride and sodium lauryl sulphate. 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 derived from material of vegetable origin. The commercially sourced proprietary film-coating mixture contains polyethylene glycol 3350, polyvinyl alcohol (partially hydrolysed), talc and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

[HA466 trade name] is white coloured, capsule shaped, film coated tablets debossed with “M 152” on one side and plain on the other side. The tablets are presented in a round, white opaque, induction-sealed HDPE bottle fitted with a white polypropylene screw cap and containing a desiccant (molecular sieve sachet) (pack size: 30 tablets).

The development of the final composition of [HA466 trade name] has been described. The objective was to develop a stable fixed-dose combination tablet, bioequivalent to the innovator products, Sustiva® 600mg Tablets, Epivir® 300mg film-coated tablets and Viread® 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.

Since the formulation comprises of three different APIs with different physicochemical properties a double layered tablet was developed, with efavirenz in one layer, and TDF and lamivudine in the other layer. 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. TDF is moisture sensitive and shows poor flow properties. The process developed for the second layer entails a dry granulation step for TDF, with lamivudine being introduced extragranularly. 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 products.

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), fumaric acid (HPLC) and of the colorant 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°C/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 2008 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of fixed dose combination of Tenofovir Disoproxil Fumarate 300mg, Lamivudine 300mg and Efavirenz 600mg Tablets of Matrix Laboratories Limited, India comparing with that of Viread® (containing tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, Inc. Foster City, CA 94404, Made in Canada, Epivir® (containing lamivudine) 300 mg tablets of GlaxoSmithKline Research Triangle Park, NC 27709, Made in England, manufactured under agreement from Shire pharmaceuticals Group Plc, Basingstoke, UK and Sustiva® (containing efavirenz) 600 mg tablets of Bristol-Myers Squibb Company, Princeton, NJ 08543 USA in healthy, adult, human subjects under fasting conditions (study no. 650/108).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600/300/300 mg fixed dose combination tablet manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the individual reference formulations (Sustiva®, Bristol-Myers Squibb Company; Epivir®, GlaxoSmithKline; Viread®, Gilead Sciences) 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 [HA466 trade name] (efavirenz 600 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg)) Batch no. 1004762.
Treatment R:	Reference 1 tablet Sustiva® (efavirenz 600 mg) Batch no. 6E22114A 1 tablet .Epivir® (lamivudine 300 mg) Batch no. R245588 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. FDB023.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 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 efavirenz, lamivudine and tenofovir disoproxil fumarate (as tenofovir) were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 100 ng/mL for efavirenz, 25 ng/mL for lamivudine, and 5 ng/mL for tenofovir.

The study was performed with 48 participants; data generated from a total of 44 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for efavirenz, lamivudine and tenofovir as well as statistical results are summarised in the following tables:

Efavirenz

	Test formulation (T)	**Reference (R)**	**log-transformed parameters**

Pharmacokinetic Parameter	arithmetic mean ± SD (geometric mean)	arithmetic mean ± SD (geometric mean)	**Ratio** T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	4.28 ± 1.61	3.81 ± 1.18	-	-
C_{max} (ng/mL)	2689 ± 785 (2588)	2895 ± 893 (2747)	94.2	85.3 – 104.1
AUC_{0-72h} (ng·h/mL)	64850 ± 21728 (61086)	69724 ± 22130 (66164)	92.3	85.8 – 99.4

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 (ANOVAlog)
t_{max} (h)	1.92 ± 0.93	1.68 ± 0.74	-	-
C_{max} (ng/mL)	2483 ± 706 (2379)	2582 ± 641 (2505)	95.0	87.0 – 103.7
AUC_{0-t} (ng·h/mL)	13139 ± 3731 (12754)	13570 ± 3258 (13156)	95.6	88.8 – 102.9
AUC_{0-inf} (ng·h/mL)	13457 ± 3717 (12916)	13889 ± 3229 (13491)	95.7	89.3 – 102.7

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)	1.17 ± 0.57	1.12 ± 0.50	-	-
C_{max} (ng/mL)	277 ± 79 (265)	283 ± 74 (267)	99.4	91.5 – 108.0
AUC_{0-t} (ng·h/mL)	2091 ± 576 (2001)	2096 ± 609 (1963)	101.9	92.9 – 111.8
AUC_{0-inf} (ng·h/mL)	2358 ± 627 (2268)	2352 ± 670 (2212)	102.5	94.1 – 111.7

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, lamivudine and tenofovir. Accordingly, the test fixed dose combination tablet [HA466 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences).

4. Summary of product safety and efficacy

[HA466 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products Sustiva® (efavirenz 600 mg tablets, Bristol-Myers Squibb Company, USA), Epivir® (lamivudine 300 mg tablets, GlaxoSmithKline, UK) and Viread® (tenofovir disoproxil fumarate 300 mg tablets, Gilead Sciences, Canada) 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 [HA466 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA466 trade name] has been shown to be bioequivalent with a combination of the three separate reference formulations: Sustiva® (efavirenz 600 mg tablets, Bristol-Myers Squibb Company, USA), Epivir® (lamivudine 300 mg tablets, GlaxoSmithKline, UK) and Viread® (tenofovir disoproxil fumarate 300 mg tablets, Gilead Sciences, Canada).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA466 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 [HA466 trade name] was acceptable for the following indication: treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing at least 40 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 [HA466 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.