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	HA500 name][*]
Manufacturer of Prequalified Product	Cipla Ltd. Unit VII, III, IV L-147 to L147-1 and L-139 to L-146 Verna Industrial Estate, Goa – 403722, India
Active Pharmaceutical Ingredients (APIs)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate.
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR06)
Therapeutic indication	[HA500 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and 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

[HA500 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and 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.

[HA500 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 Ingredients (APIs)

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 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.

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

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
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 key intermediate in the multi-step synthesis process of emtricitabine, with L-menthol as the starting material for synthesis. The enantiomer of emtricitabine is controlled at level of not more than 0.3% by chiral HPLC chromatography.

Emtricitabine is known to exhibit polymorphism and exists in Forms I, II and III. According to XRPD and DSC data Form I is consistently produced.

The API specifications include description, solubility, identification (IR and HPLC), loss on drying, residue on ignition, heavy metals, colour of solution, enantiomeric purity (chiral HPLC), assay (HPLC), residual solvents, particle size distribution, polymorphic identity (DSC and XRPD), specific optical rotation and chromatographic purity (HPLC).

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

Tenofovir disoproxil fumarate
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. TDF is a BCS Class 3 API, i.e. of high solubility and low permeability.

TDF is manufactured from (R)-9-[2-(phosphonylmethoxy) propyl] adenine (R-PMPA or tenofovir), which is commercially obtained. The specifications of R-PMPA, which is in turn obtained from adenine via (R)-9-(2-hydroxypropyl) adenine, are considered adequate for the manufacturing of TDF. The structure and stereochemistry of TDF was confirmed by the route of synthesis, with retention of chirality, and spectrometric data.

The specifications for TDF include description, solubility, clarity and colour of solution, identification of TDF and fumaric acid, assay and fumaric acid content by HPLC, chromatographic purity (HPLC), heavy metals, water content, residual solvents and particle size. The limits of the related substances are in agreement with 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 at $\leq$ 5.0 ppm. Two polymorphic forms have been identified for TDF. Polymorph I is controlled by DSC and x-ray powder diffraction. 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 the API is stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include corn starch, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide red, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The commercially sourced proprietary film-coating mixture contains hypromellose, iron oxide red, iron oxide yellow, lecithin (soya), polyvinyl alcohol (partially

hydrolysed), talc, titanium dioxide and xanthan gum. Assurance by means of certificates was provided that the excipients are BSE/TSE free.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600mg/200mg/300mg Tablets are pink coloured, capsule shaped, biconvex, film-coated tablets. The tablets are presented in a round, white opaque, induction-sealed HDPE bottle fitted with white polypropylene screw cap closure and containing three silica gel desiccant bags (pack size: 30 tablets).

The development of the final composition of the product has been described. The objective was to obtain a stable fixed-dose combination tablet, bioequivalent to the comparator product, Atripla® film-coated tablets. Similar to the comparator product, a bilayered tablet containing the BCS low soluble efavirenz in one layer and the highly soluble emtricitabine and TDF in the other layer was developed, targeting the dissolution characteristics of the comparator. The excipients were selected based on prior experience and taking into account the qualitative composition of the comparator product, supported by compatibility studies.

Both tablet layers are obtained through wet granulation, using non-aqueous granulation for the emtricitabine/TDF layer, the latter APIs being susceptible to hydrolysis. Degradation is furthermore limited by control of the tablet moisture content and by protective primary packaging, which includes a silica gel desiccant. The process parameters were optimised to obtain tablets of desired characteristics, with dissolution profiles similar to that of the comparator product. Validation data were presented for primary batches, demonstrating the consistency of the process and the quality of the product. Satisfactory in-process controls have been established.

Product 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), average weight, water content, uniformity of dosage units, dissolution (HPLC detection), degradation products (HPLC), assay (HPLC), residual solvents and microbiological examination of non-sterile products. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been conducted 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. The data showed some degradation for TDF and also emtricitabine, though all parameters were well within the agreed limits 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 2008 according to internationally accepted guidelines.

A randomized, balanced, open label, single dose, two-treatment, two-period, two-sequence, crossover, truncated bioequivalence study comparing the Fixed Dose Combination (FDC) of Tenofovir disoproxil fumarate, Emtricitabine and Efavirenz Tablets containing 300 mg Tenofovir disoproxil fumarate, 200 mg Emtricitabine and 600 mg Efavirenz of Cipla Limited, India with Atripla®(Tenofovir disoproxil fumarate, Emtricitabine and Efavirenz) Tablets containing 300 mg Tenofovir disoproxil fumarate, 200

mg Emtricitabine and 600 mg Efavirenz of Bristol-Myers Squibb and Gilead Sciences Inc., USA in 72 healthy adult human subjects under fasting conditions (study no. BBRC/US/08/001).

The objective of the study was to compare the bioavailability of the stated Tenofovir disoproxil fumarate/Emtricitabine/Efavirenz 300/200/600 mg tablet manufactured by Cipla Limited, India(test drug) with the same dose of the reference formulation (Atripla™ 300/200/600 mg tablet, Bristol-Myers Squibb) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – Tenofovir disoproxil fumarate/Emtricitabine/Efavirenz 300/200/600 mg tablet
(tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + efavirenz 600 mg)
Batch no. X80226.

Treatment R: References
– Atripla™300/200/600 mg tablet
(tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + efavirenz 600 mg)
Batch no. V0129A007.

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 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max}. Drug concentrations for tenofovir, emtricitabine and efavirenz were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/ml for tenofovir, 25 ng/ml for emtricitabine and 50 ng/ml for efavirenz.

The study was performed with 72 participants; data generated from a total of 68 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.3 ± 0.7	1.3 ± 0.6	-	-
C_{max} (ng/ml)	258 ± 96 (241)	267 ± 103 (249)	96.5	90.6 – 102.8
AUC_{0-t} (ng.h/ml)	1483 ± 512 (1403)	1585 ± 588 (1487)	94.4	89.1 – 99.9
AUC_{0-inf} (ng.h/ml)	1843 ± 534 (1770)	1972 ± 692 (1874)	94.5	89.9 – 99.3

* geometric mean

Emtricitabine

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)	2.1 ± 0.8	1.9 ± 0.7	-	-
C_{max} (ng/ml)	1617 ± 446 (1561)	1711 ± 412 (1663)	93.9	89.5 – 98.5

AUC_{0-t} (ng.h/ml)	8845 ± 2055 (8613)	9260 ± 2343 (8984)	95.9	92.6 – 99.3
AUC_{0-inf} (ng.h/ml)	9197 ± 2015 (8984)	9649 ± 2594 (9359)	96.0	92.8 – 99.3

* geometric mean

Efavirenz

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)	4.3 ± 1.5	4.0 ± 1.1	-	-
C_{max} (ng/ml)	1984 ± 676 (1879)	1974 ± 794 (1846)	101.8	96.1 – 107.8
AUC_{0-72h} (ng.h/ml)	50085 ± 20356 (46008)	47330 ± 20992 (43277)	106.3	101.9 – 110.9

* geometric mean

Conclusion

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max}values regarding tenofovir, emtricitabine and efavirenz. Accordingly, the test [HA500 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Atripla™ 300/200/600 mg tablet (Bristol-Myers Squibb).

4. Summary of Product Safety and Efficacy

[HA500 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required for the innovator product. According to the submitted data on quality and bioavailability [HA500 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Atripla™ tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.) 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 [HA500 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA500 trade name] has 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, [HA500 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [HA500 trade name] was acceptable for the following indication: **"treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents 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 has advised that the quality, efficacy and safety of [HA500 trade name] allow inclusion of [HA500 trade name], manufactured at Cipla Ltd., Unit VII, III, IV, L-147 to L147-1 and L-139 to L-146, Verna Industrial Estate,Goa – 403722, India in the list of prequalified medicinal products.