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	[HA593 trade name][*]
Manufacturer of Prequalified Product	Cipla limited Unit II, A-42, MIDC Patalganga District-Raigad Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz, lamivudine and tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR06)
Therapeutic indication	[HA593 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.

1. Introduction

[HA593 trade name] is indicated in treatment of HIV, as detailed in the summary of product characteristics.

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 show that efavirenz is of BCS low solubility in aqueous medium over the physiological pH range.

Efavirenz is manufactured in several steps from a commercially available starting material. It can exist in a number of crystalline forms. Form I is consistently produced as controlled with DSC. The micronized form is used in the manufacture of the FPP.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, UV), polymorphic identity (DSC), residue on ignition, heavy metals, completeness of solution, water content (KF), specific optical rotation, organic impurities (HPLC), enantiomeric purity (chiral HPLC; 0.5%), assay (HPLC), residual solvents, particle size distribution and loss on drying.

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

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 packaging.

Lamivudine

Based on scientific principles the WHO PQP has identified lamivudine (up to 300mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus highly soluble over the pH range 1 to 6.8.

Lamivudine is described in the Ph.Int., Ph.Eur. and the USP, and is considered well-established in the WHO PQP.

The specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR, HPLC), polymorphic identity (XRPD), light absorption, water content (KF), limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), related compounds (HPLC), assay (HPLC), residue on ignition, heavy metals, specific optical rotation, methane sulfonates (≤ 5 ppm each), tapped density and residual solvents.

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 packaging.

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. The pro-drug has increased oral bioavailability compared to tenofovir.

TDF, (R)-9-(2-phosphonomethoxypropyl) adenine disoproxil fumarate, is manufactured in several 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 TDF specifications include tests for description, solubility, identification of the API (IR, HPLC) and fumaric acid (HPLC), polymorphic identity (DSC, XRPD), clarity and colour of solution, heavy metals, water content (KF), related substances (HPLC, GC), S-isomer content (chiral HPLC; ≤ 1.0%), assay (HPLC), fumaric acid content, residual solvents and particle size. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int. 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 packaging.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, hydroxypropylcellulose, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulphate and iron oxide yellow. Magnesium stearate is of vegetable origin. The seal coat contains hypromellose and the commercially sourced proprietary film-coating mixture contains polyvinyl alcohol – part hydrolysed, talc, titanium dioxide, macrogol/PEG 3350, lecithin (soya) and iron oxide yellow.

Finished pharmaceutical product (FPP)

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

The multisource product is a yellow coloured, capsule shaped, biconvex, film coated tablet with "T" debossed on one side and plain on other side. The tablets are packaged in an HDPE bottle with non-CRC HDPE cap, containing a silica gel desiccant.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator products: Sustiva® (efavirenz) 600mg tablets, Epivir® (lamivudine) 300mg tablets and Viread® (TDF) 300mg tablets. Due to incompatibility between efavirenz and TDF a bilayer tablet, containing the BCS low soluble efavirenz in one layer and lamivudine and TDF in the other layer, was developed. The excipients were selected based on prior experience, their functional properties and excipients present in the individual comparator products, supported by compatibility studies.

The efavirenz tablet is obtained via a wet granulation process. The lamivudine/TDF layer is obtained via dry granulation processes, protecting TDF form degradation. To protect the product from moisture a silica gel desiccant is included in the bottle packs. During process development the manufacturing steps and critical process parameters that controlled factors required to reach the quality target product profile were identified and optimised. Satisfactory in-process controls have been established.

Specifications
The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average weight, disintegration time, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), degradation products (HPLC), assay (HPLC), residual solvents and microbial limits. The test methods have been satisfactorily validated.

Stability testing
Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed slight degradation for TDF, 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 2012 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of efavirenz/lamivudine/tenofovir disoproxil fumarate 600/300/300 mg tablets of Cipla Ltd., India with three individual reference products, Viread® (tenofovir disoproxil fumarate 300 mg) tablet of Gilead Sciences, Inc., USA, Epivir® (lamivudine 300 mg) tablet of GlaxoSmithKline, USA and Sustiva® (efavirenz 600 mg) tablet of Bristol-Myers Squibb Company, USA in normal, healthy, adult, human subjects under fasting condition (study no. ARL/10/056).

The objective of the study was to compare the bioavailability of the stated efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/300mg tablets manufactured by Cipla Ltd., India (test drug) with the individual reference formulations Viread® (Gilead Sciences), Epivir® (GlaxoSmithKline) and Sustiva® (Bristol-Myers Squibb Company) 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 – 1 tablet of efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/300mg
(tenofovir disoproxil fumarate 300mg + lamivudine 300 mg + efavirenz 600mg)
Batch no. KW1D17

Treatment R: References –
- 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg), batch no. 02006893
- 1 tablet Epivir®(lamivudine 300 mg), batch no. 9L004
- 1 tablet Sustiva® (efavirenz 600 mg), batch no. 9B54552A

A 32-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 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 tenofovir, lamivudine and efavirenz were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 10 ng/mL for tenofovir, about 50 ng/ml for lamivudine and about 80 ng/mL for efavirenz.

The study was performed with 48 participants; data generated from a total of 45 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.02 ± 0.30	0.91 ± 0.27	-	-
C_{max} (ng/ml)	336 ± 82 (327)	341 ± 83 (333)	98.2	93.2 – 103.5
AUC_{0-t} (ng.h/ml)	2311 ± 654 (2231)	2266 ± 553 (2211)	100.9	96.3 – 105.7
AUC_{0-inf} (ng.h/ml)	2688 ± 694 (2612)	2632 ± 615 (2572)	101.6	97.3 – 106.0

* geometric mean

Lamivudine

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)	1.38 ± 0.50	1.30 ± 0.39	-	-
C_{max} (ng/ml)	2865 ± 747 (2791)	2876 ± 597 (2813)	99.2	93.6 – 105.2
AUC_{0-t} (ng.h/ml)	12934 ± 2998 (12642)	12310 ± 2595 (12065)	104.8	99.4 – 110.5
AUC_{0-inf} (ng.h/ml)	13312 ± 3000 (13029)	12685 ± 2619 (12442)	104.7	99.5 – 110.2

* 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)	3.71 ± 1.24	3.65 ± 1.03	-	-
C_{max} (ng/ml)	3112 ± 752 (3016)	2825 ± 863 (2694)	112.0	104.4 – 120.0
AUC_{0-72h} (ng.h/ml)	61667 ± 16044 (59177)	57119 ± 15619 (54476)	108.6	102.3 – 115.4

* geometric mean

Conclusions

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding tenofovir, lamivudine and efavirenz. Accordingly, the test FDC tablet efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/300mg tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual references Viread® (Gilead Sciences Inc.), Epivir® (GlaxoSmithKline) and Sustiva® (Bristol-Myers Squibb Company).

4. Summary of Product Safety and Efficacy

[HA593 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [HA593 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual innovator products Viread®, Epivir® and Sustiva® 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 taken into account. 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 [HA593 trade name] are used in accordance with the SmPC.

Bioequivalence

[HA593 trade name] has shown to be bioequivalent with individual innovator products Viread® (Gilead Sciences, Inc., USA), Epivir® (GlaxoSmithKline, USA) and Sustiva® (Bristol-Myers Squibb Company, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA593 trade name] are 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 [HA593 trade name] was acceptable for the following indication: **"treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 35 kg."** and has advised that the quality, efficacy and safety of [HA593 trade name] allow inclusion of [HA593 trade name], manufactured at Cipla Ltd, Unit II, A-42, MIDC, Patalganga, District-Raigad, Maharashtra, India, in the list of prequalified medicinal products.