This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300 mg Tablets *
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block No. 2 Village Theda P.O. Lodhi Majra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, INDIA
Active Pharmaceutical Ingredients(APIs):	Efavirenz, lamivudine, tenofovir disoproxil fumarate.
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR11)
Therapeutic indication:	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing ≥ 35 kg).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing ≥ 35 kg).

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets should be prescribed by a health care provider 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 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 low solubility according to the BCS in aqueous medium over the pH range 1.2 to 7.2.

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 characterised by DSC.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC, UV), completeness of solution, water content (KF), residue on ignition, heavy metals, organic impurities (HPLC), limit of efavirenz enantiomer (chiral HPLC; ≤ 0.2%), assay (HPLC), specific optical rotation, melting range (DSC), residual solvents, particle size distribution and bulk density.

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

Lamivudine

Based on scientific principles the WHO Prequalification of Medicines Programme has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus highly soluble in aqueous medium over the pH range 1.0 – 6.8.

Lamivudine API is described in the Ph.Int., Ph.Eur. and USP, and is considered well-established in the Prequalification Programme.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), light absorption, water content (KF), heavy metals, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), chromatographic purity (HPLC), assay (HPLC), residual solvents, bulk density and particle size.

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 is of BCS high solubility.

TDF 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, melting range, water content (KF), heavy metals, residue on ignition, fumaric acid content, related substances (HPLC), assay (HPLC), enantiomeric purity (S-isomer $\leq$ 0.2%), residual solvents, particle size, polymorphic form (XRPD) and bulk density. 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.

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 monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer, pregelatinized starch and sodium lauryl sulfate. The film-coat contains lactose monohydrate, hypromellose, titanium dioxide and triacetin. TSE / BSE free certificates have been provided for the excipients.

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 white to off-white, capsule shaped, biconvex film coated tablet plain on both sides. The tablets are packaged in an HDPE bottle with polypropylene closure, containing two silica gel desiccant sachets.

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. A bilayer tablet containing the BCS low soluble efavirenz in one layer and the highly soluble emtricitabine and TDF in the other layer was developed. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information of the qualitative composition of the comparator products and compatibility with the APIs.

Wet granulation was selected to overcome the poor flow properties of the APIs. The efavirenz layer was prepared using aqueous wet granulation while the layer of emtricitabine and TDF was prepared using non-aqueous wet granulation. Studies were conducted using varying concentration of excipients to study the robustness and also to optimize the concentration of functional excipients in order to arrive at a composition with desired dissolution profile. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and

TLC) and colorant, average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvent (GC) 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.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2013 according to internationally accepted guidelines.

Bioequivalence study of single dose of fixed dose combination of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets manufactured by Macleods Pharmaceuticals Ltd., India in comparison with separate formulations of SUSTIVA® (efavirenz) tablets 600 mg distributed by Bristol-Mayer-Squibb, USA, EPIVIR® (lamivudine) tablets 300 mg manufactured by GlaxoSmithKline, USA and Viread® (tenofovir disoproxil fumarate) tablets 300 mg manufactured for Gilead Sciences, Inc., USA in healthy, adult, human subjects under fasting condition. (study no. BEQ-679-ELT(F)-2011).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets manufactured by Macleods Pharmaceuticals 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 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600mg/300mg/300mg (efavirenz 600mg+ lamivudine 300 mg + tenofovir disoproxil fumarate 300mg) Batch no. BEZ202A.
Treatment R:	References – 1 tablet Sustiva® (efavirenz 600 mg) Batch no. 1M47404A 1 tablet Epivir® (lamivudine 300 mg) Batch no. 2ZP3378 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. 000878.

A 35 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 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 were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 50 ng/ml for efavirenz, about 50 ng/ml for lamivudine and about 5 ng/ml for tenofovir.

The study was performed with 40 participants; data generated from a total of 30 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

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)	3.88 ± 1.23	3.97 ± 1.13	-	-
C_{max} (ng/ml)	2807 ± 690 (2704)	2830 ± 760 (2751)	98.3	89.7 – 107.7
AUC_{0-72h} (ng.h/ml)	59886 ± 15754 (57392)	59975 ± 15710 (57703)	99.5	95.0 – 104.1

* 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)	1.62 ± 0.70	1.14 ± 0.30	-	-
C_{max} (ng/ml)	3099 ± 709 (3027)	3358 ± 777 (3298)	91.8	85.1 – 99.0
AUC_{0-t} (ng.h/ml)	15273 ± 3382 (14882)	14495 ± 3331 (14271)	104.3	97.4 – 111.7
AUC_{0-inf} (ng.h/ml)	15640 ± 3420 (15259)	14852 ± 3350 (14634)	104.3	97.6 – 111.4

* geometric mean

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)	1.38 ± 0.55	0.96 ± 0.31	-	-
C_{max} (ng/ml)	320 ± 94 (309)	341 ± 79 (334)	92.6	87.2 – 98.4

AUC_{0-t} (ng.h/ml)	2697 ± 633 (2631)	2584 ± 690 (2526)	104.2	99.4 – 109.2
AUC_{0-inf} (ng.h/ml)	2946 ± 747 (2865)	2782 ± 690 (2731)	104.9	100.6 – 109.5

* geometric mean

Conclusions

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 FDC tablet Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600mg/300mg/300mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual references, Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.).

4. Summary of Product Safety and Efficacy

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets 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 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual innovator products, Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.) 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 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets is used in accordance with the SmPC.

Bioequivalence

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets has shown to be bioequivalent with the individual innovator products, Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets 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 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets 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 ≥ 35 kg"** and has advised that the quality, efficacy and safety of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets allow inclusion of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg / 300 mg/300mg Tablets, manufactured at Macleods Pharmaceuticals Limited, Block No.2 Village Theda, P.O. Lodhi Majra

Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.