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:	[HA714 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block N 2 Village Theda P.O. Lodhi Majra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient (API):	Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations; J05AR11 lamivudine, tenofovir disoproxil fumarate and efavirenz
Therapeutic indication:	[HA714 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection in patients weighing at least 30 kg

1. Introduction

[HA714 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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 and Lamivudine

Efavirenz and lamivudine have been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that efavirenz and lamivudine, used in the manufacture of [HA714 trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 400 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 pink-coloured, capsule-shaped, biconvex, film-coated tablet, plain on both sides. The tablets are packaged in either a white, round HDPE bottle with polypropylene continuous thread closure with pulp and white printed heat seal liner, containing three silica gel desiccant sachets or a white, round HDPE bottle with polypropylene child-resistant closure, with pulp and white printed heat seal liner 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: efavirenz USP 200mg tablets (Mylan Laboratories Ltd, India), Epivir® (lamivudine) 300mg tablets and Viread® (tenofovir disoproxil fumarate) 300mg tablets. A bilayer tablet containing the BCS low soluble efavirenz in one layer and the highly soluble emtricitabine and tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate 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.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

Single dose fasting in-vivo bioequivalence study of fixed dose combination of efavirenz / lamivudine / tenofovir disoproxil fumarate tablets 400 mg/300 mg/300 mg (Macleods Pharmaceuticals Ltd., India) in comparison with separate formulation of two tablets of Efavirenz tablets USP 200 mg (Mylan Laboratories Ltd., India), one tablet of Epivir® (lamivudine) tablets 300 mg (GlaxoSmithKline, USA) and one tablet of Viread® (tenofovir disoproxil fumarate) tablets 300 mg (Gilead Sciences, Inc., USA) in healthy, adult, human subjects (study no. BEQ-1748-ELT(F)-2016).

The objective of the study was to compare the bioavailability of the stated efavirenz / lamivudine / tenofovir disoproxil fumarate 400mg/300mg/300 mg FDC tablet manufactured by/for Macleods Pharmaceuticals Limited, India (test drug) with the reference formulations efavirenz USP 200 mg tablets (Mylan Laboratories Ltd., India), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.) 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 400 mg/ 300 mg/ 300 mg
(efavirenz 400mg + lamivudine 300mg + tenofovir disoproxil fumarate 300mg)
Batch no. BEB3601A

Treatment R: Reference
– 2 tablets Efavirenz tablets USP 200 mg (efavirenz 400 mg)
Batch no. 3055579.
– 1 tablet Epivir® (lamivudine 300 mg)
Batch no. 5ZP1465.
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg)
Batch no. 005874.

A 36-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 28 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 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,50 ng/mL for lamivudine and 5 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 33 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)	3.1 ± 1.5	3.3 ± 1.4	-	-
C_{max} (ng/mL)	1924 ± 528 (1848)	1741 ± 515 (1666)	110.9	102.6 – 120.0
AUC_{0-72h} (ng.h/mL)	36975 ± 9104 (35847)	36375 ± 8817 (35248)	101.7	96.5 – 107.2

* 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)[#]	1.7 ± 0.9	1.6 ± 1.0	-	-
C_{max} (ng/mL)	2505 ± 655 (2410)	2627 ± 620 (2540)	94.9	88.6 – 101.5
AUC_{0-t} (ng.h/mL)	12063 ± 2720 (11738)	11834 ± 2617 (11533)	101.8	94.3 – 109.9
AUC_{0-inf} (ng.h/mL)	12434 ± 2695 --	12189 ± 2617 --	-	-

* 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)[#]	1.4 ± 0.8	1.1 ± 0.5	-	-
C_{max} (ng/mL)	267 ± 70 (258)	286 ± 78 (275)	93.8	88.1 – 99.9
AUC_{0-t} (ng.h/mL)	2153 ± 610 (2059)	2151 ± 552 (2073)	99.3	92.7 – 106.4
AUC_{0-inf} (ng.h/mL)	2370 ± 629 --	2382 ± 527 --	-	-

* geometric mean

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 efavirenz, lamivudine and tenofovir. Accordingly, the test efavirenz/ lamivudine/ tenofovir disoproxil fumarate 400mg/300mg/300mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations efavirenz USP 200 mg tablets (Mylan Laboratories Ltd., India), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.).

4. Summary of Product Safety and Efficacy

[HA714 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, [HA714 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference formulations Efavirenz USP 200 mg (Mylan Laboratories Ltd., India), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA714 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 [HA714 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA714 trade name] has been shown to be bioequivalent with efavirenz USP 200 mg tablets (Mylan Laboratories Ltd., India), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA714 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 [HA714 trade name] was acceptable for the following indication**: "the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 30 kg"** and has advised that the quality, efficacy and safety of [HA714 trade name] allow inclusion of [HA714 trade name], 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.