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	[HA562 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase II & Phase III, Unit II Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210, India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz, emtricitabine and tenofovir disoproxil fumarate.
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (emtricitabine, tenofovir disoproxil fumarate and efavirenz: J05AR06)
Therapeutic indication	[HA562 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

[HA562 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.

[HA562 trade name] should be initiated by a healthcare 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 Ingredient (API)

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 8.0.

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

Efavirenz is manufactured in several steps from a commercially available starting material. It can exist in a number of crystalline forms, which were characterised by X-ray powder diffraction (XRPD). Form I is consistently produced.

The API specifications 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.

Emtricitabine

Based on scientific principles the WHO Prequalification Team-Medicines has identified emtricitabine (up to 200 mg oral dose) as a BCS class 1 API. Emtricitabine is thus highly soluble according to the BCS.

Emtricitabine, 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone, has two chiral centres. The desired stereochemistry is built into the key intermediate in the multi-step synthesis of emtricitabine. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications include tests for description, solubility, identification (IR, HPLC, specific optical rotation), loss on drying, sulfated ash, heavy metals, related substances (HPLC), enantiomer/epimer content (chiral HPLC), assay (HPLC), residual solvents, particle size, polymorphic identity and boron content.

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. 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 specifications for TDF are pharmacopoeial based and 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 microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, pregelatinized starch and magnesium stearate. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol (part-hydrolysed), titanium dioxide, polyethylene glycol, talc, red iron oxide and black iron oxide. 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.

The multisource product is a pink, capsule shaped, biconvex, film-coated tablet debossed with “CL 81” on one side and plain on the other side. The tablets are packaged in an HDPE bottle with child resistant polypropylene closure, also containing a sachet filled with silica gel as desiccant.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator product, Atripla®. Similar to the comparator product, 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 product and compatibility with the APIs.

Critical quality attributes, such as particle size of efavirenz and API flow properties, were identified for selection of the manufacturing process. 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. The process parameters were optimised to obtain tablets of desired characteristics, with dissolution profiles similar to that of the comparator 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), 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 storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was observed for TDF, though the related substances content remained within acceptable limits. 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 2011/2012 according to internationally accepted guidelines.

Bioequivalence study of single dose of fixed dose combination of [HA562 trade name] (each tablet contains efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Atripla® (efavirenz 600mg/emtricitabine 200mg/tenofovir Disoproxil Fumarate 300mg) tablets (each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil) manufactured for Bristol-Myers Squibb and Gilead Sciences, USA in healthy, adult, human subjects under fasting condition (study no. BEQ-701-EET(F)-2011).

The objective of the study was to compare the bioavailability of the stated [HA562 trade name] FDC tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Atripla® (Bristol-Myers Squibb and 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 [HA562 trade name]
(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. EEA5101A
Treatment R: Reference – 1 tablet Atripla®
(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 02009674

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, emtricitabine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 50 ng/mL for efavirenz as well as for emtricitabine and about 5 ng/mL for tenofovir.

The study was performed with 42 participants; data generated from a total of 38 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Efavirenz

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)	3.43 ± 1.26	3.76 ± 1.34	–	–
C_{max} (ng/mL)	2401 ± 743 (2295)	2246 ± 727 (2120)	108.2	99.7-117.5
AUC_{0-72h} (ng·h/mL)	56539 ± 18060 (53841)	52230 ± 17895 (49093)	109.7	101.5-118.5

Emtricitabine

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)	1.80 ± 0.85	1.63 ± 0.64	–	–
C_{max} (ng/mL)	2191 ± 527 (2116)	2194 ± 443 (2144)	98.7	92.5 – 105.3
AUC_{0-t} (ng·h/mL)	10475 ± 2101 (10260)	10389 ± 1895 (10217)	100.4	95.3 – 105.8
AUC_{0-inf} (ng·h/mL)	10895 ± 2094 (10688)	10837 ± 1890 (10672)	100.2	95.4 – 105.1

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)	1.47 ± 0.74	41.28 ± 0.48	–	–
C_{max} (ng/mL)	289 ± 73 (279)	296 ± 72 (288)	96.9	90.3 – 103.8
AUC_{0-t} (ng·h/mL)	2253 ± 542 (2197)	2231 ± 523 (2181)	100.7	94.7 – 107.2
AUC_{0-inf} (ng·h/mL)	2463 ± 563 (2411)	2447 ± 530 (2403)	100.3	94.2 – 106.9

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, emtricitabine and tenofovir. Accordingly, the test FDC tablet [HA562 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Atripla® (Bristol-Myers Squibb/Gilead Sciences Inc. U.S.A.).

4. Summary of product safety and efficacy

[HA562 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, [HA562 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Atripla® tablet (Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA562 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 [HA562 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA562 trade name] has been 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, [HA562 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 [HA562 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 would allow inclusion of [HA562 trade name], manufactured at Macleods pharmaceuticals limited, Phase II and Phase III, Unit II, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman-396210, India in the list of prequalified medicinal products.