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	[HA538 trade name]*
Manufacturer of Prequalified Product	Hetero Labs Limited Unit – V, Sy No. 439, 440, 441 & 458 TSIIC Formulation SEZ Polepally village, Jadcherla Mandal, Mahaboob Nagar District Telangana, India.
Active Pharmaceutical Ingredients (APIs)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate.
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (emtricitabine, tenofovir disoproxil fumarate and efavirenz: J05AR06)
Therapeutic indication	[HA538 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

[HA538 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.

[HA538 trade name] should be initiated 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 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 in the dossier show that efavirenz is practically insoluble 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 a two-step process from a commercially available starting material. Efavirenz can exist in several crystalline forms. Form I, characterized by X-ray powder diffraction, is consistently produced.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification (IR and UV), polymorphic form (XRPD), water content, residue on ignition, heavy metals, completeness of solution, organic impurities (HPLC), assay (HPLC), limit of efavirenz enantiomer (chiral HPLC; ≤ 0.15%), particle size distribution, residual solvents and determination of metal impurities (ICP-MS).

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

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) 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 process, with L-menthol as the starting material for synthesis. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications are Ph.Int. based and include tests for description, solubility, identification (IR and SOR), polymorphic identity (XPRD), loss on drying, sulfated ash, heavy metals, enantiomeric content (chiral HPLC; ≤ 0.3%), related substances (HPLC), assay (potentiometry), residual solvents, particle size, microbiological examination and content of mesilates (GC-MS; each individual ≤ 7.5 ppm).

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 BCS high soluble.

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 specifications for TDF include tests for description, solubility, identification (IR and HPLC), clarity of solution, water content, heavy metals, XRPD, melting point (DSC), related compounds (HPLC), enantiomeric impurity (≤ 0.40%; chiral HPLC), assay and fumaric acid content (HPLC), residual solvents, particle size and microbiological examination. The mutagenic 9-propenyladenine, which is a synthesis related substance, is controlled at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int.

TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114ºC) and a high melting form (m.p. 114-118ºC). The high melting form, controlled by XRPD and melting point determination, is consistently produced.

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, sodium lauryl sulfate, hydroxypropyl cellulose and magnesium stearate. The

commercially sourced proprietary film-coating mixture contains polyvinyl alcohol (partly hydrolysed), titanium dioxide, macrogol/PEG, talc, iron oxide red and iron oxide black. 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 coloured, capsule-shaped, film-coated tablet debossed with 'H' on one side and '128' on the other side. The tablets are packaged in an HDPE bottle closed with polypropylene continuous thread cap with pulp liner and containing a 2.0g silica gel desiccant.

The aim of formulation development was to obtain a stable fixed-dose combination tablet, bioequivalent to the comparator product, Atripla® film-coated tablets. 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 excipients selected for the core tablets are commonly used in tablets, qualitatively similar to that of the comparator product and supported by compatibility studies. The comparator product was characterised for its physical and chemical properties to define a quality target product profile.

Based on the stability of APIs towards hydrolysis, it was decided to prepare the efavirenz blend by a wet granulation process and the emtricitabine and tenofovir DF blend by a dry granulation process and compress into bilayer tablets. To protect the product from moisture a silica gel desiccant is included in the bottle packs. 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 include tests for description, identification of the APIs (HPLC and TLC), average weight, water content, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related compounds (HPLC), assay (HPLC) and microbiological examination. The test methods have been adequately 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 2010/2011 according to internationally accepted guidelines:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose bioequivalence study of [HA538 trade name] (containing efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) of Hetero Labs Limited, India comparing with ATRIPLA® tablets (containing efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil

fumarate 300 mg) manufactured for Bristol-Myers Squibb & Gilead Sciences, LLC Foster City, CA 94404, USA in healthy, adult, human subjects, under fasting conditions (study no. BE-315-EFET-2010).

The objective of the study was to compare the bioavailability of the stated [HA538 trade name] fixed dose combination tablet manufactured by Hetero Labs Limited, India (test drug) with the same dose of the reference formulation (Atripla®, Bristol-Myers Squibb & 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 – 1tablet [HA538 trade name]
(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300mg)
Batch no. J100129.

Treatment R: Reference – 1 tablet Atripla®
(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300mg)
Batch no. 02007481.

A 22 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 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 a validated LC-MS/MS method. The limit of quantification was stated to be about 40 ng/mL for efavirenz, 25 ng/mL for emtricitabine and 10 ng/mL for tenofovir.

The study was performed with 44 participants; data generated from a total of 43 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)	3.94 ± 2.12	3.99 ± 1.58	–	–
C_{max} (ng/mL)	2260 ± 703 (2142)	2442 ± 1014 (2249)	95.5	89.0 – 102.3
$AUC_{0\text{-}72h}$ (ng·h/mL)	49772 ± 12992 (47949)	51546 ± 18221 (48609)	98.9	93.8 – 104.1

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)	1.95 ± 0.84	1.95 ± 0.62	–	–
C_{max} (ng/mL)	1766 ± 445 (1716)	1661 ± 394 (1613)	106.3	100.2 – 112.6
AUC_{0-t} (ng·h/mL)	9288 ± 1661 (9147)	9065 ± 1928 (8869)	103.1	99.3 – 107.1
AUC_{0-inf} (ng·h/mL)	9625 ± 1717 (9482)	9436 ± 1972 (9239)	102.6	98.9 – 106.5

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)	1.35 ± 0.77	1.54 ± 0.56	–	–
C_{max} (ng/mL)	249 ± 95 (233)	236 ± 91 (220)	105.5	99.3 – 112.4
AUC_{0-t} (ng·h/mL)	1476 ± 565 (1382)	1488 ± 597 (1381)	100.1	92.2 – 108.6
AUC_{0-inf} (ng·h/mL)	1804 ± 577 (1722)	1861 ± 605 (1769)	97.4	90.7 – 104.6

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 fixed dose combination tablet [HA538 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).

4. Summary of product safety and efficacy

[HA538 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, [HA538 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 [HA538 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 [HA538 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA538 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, [HA538 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 [HA538 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 [HA538 trade name], manufactured at Hetero Labs Limited, (Unit V) Sy No 439, 440, 441 & 458, TSIIC Formulation SEZ, Polepally village, Jadcherla Mandal, Mahaboob Nagar District, Telangana, India in the list of prequalified medicinal products.