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	[HA553 trade name][*]
Manufacturer of Prequalified Product	Strides Shasun Limited KRS Gardens Tablet Block 36/7, Suragajakkanahalli Indlavadi Cross Anekal Taluk Bangalore – 562 106 India
Active Pharmaceutical Ingredient(s) (API)	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	[HA553 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

[HA553 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.

[HA553 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 show that efavirenz is practically insoluble in aqueous medium over the physiological pH range.

[*] 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. Form I is consistently produced as controlled with DSC.

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

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.

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 process, with L-menthol as the starting material for synthesis. 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), melting range, loss on drying, residue on ignition, heavy metals, limit of enantiomer (chiral HPLC; ≤ 0.3%), related substances (HPLC), assay (HPLC), residual solvents, particle size distribution, foreign matter, bulk density and content of alkyl methane sulfonates (each individual ≤ 3 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 packaging.

Tenofovir disoproxil fumarate (TDF)

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 specifications for TDF include tests for description, solubility, identification of the API (IR, HPLC) and fumaric acid (HPLC), melting range, residue on ignition, heavy metals, water content (KF), related substances (HPLC), S-isomer content (chiral HPLC; ≤ 1.0%), assay (HPLC), fumaric acid content, residual solvents, foreign matter, particle size and clarity of solution. 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.

TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114^{0}C) and a high melting form (m.p. 114-118^{0}C). The high melting form, controlled by melting point, is consistently produced. 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 microcrystalline cellulose, lactose, croscarmellose sodium, sodium lauryl sulfate, hydroxypropyl cellulose and magnesium stearate. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol – partly hydrolysed, macrogol/PEG, titanium dioxide, talc and FD&C Blue #2/Indigo carmine aluminium lake.

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.

The multisource product is a blue coloured, capsule shaped, biconvex film-coated tablet engraved TEE on one side and plain on the other side. The tablets are packaged in an HDPE bottle with HDPE screw closure and 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 product, Atripla®. Similar to the comparator product, a bilayer tablet containing the BCS low soluble efavirenz in one layer and the BCS 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. Based on the stability and flow properties of the APIs 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 furthermore 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 (HPLC and TLC), average weight, uniformity of weight, uniformity of dosage units (by content uniformity), tablet dimensions, moisture content (KF), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) and microbial limits. The test methods have been satisfactorily validated

Stability testing

Stability studies have been conducted at 25°C/60%RH, 30°C/65%RH and 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. Degradation was observed and the studies showed that the product should be protected from exposure to temperatures above 30ºC and to high relative humidity. 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 2009 according to internationally accepted guidelines.

A randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate tablets [600/200/300 mg] of Strides Shasun Limited, India with ATRIPLA™ (efavirenz 600 mg / emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg) tablets of Bristol-Myers Squibb & Gilead Sciences, USA in normal, healthy, adult, male and female human subjects under fasting condition (study no. ARL/09/315).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300 mg FDC tablet manufactured by Strides Shasun 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 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/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300mg

(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 7208715.

Treatment R: Reference – 1 tablet Atripla®

(efavirenz 600 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)

Batch no. FEG018A.

A 24 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 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, 35 ng/ml for emtricitabine and 10 ng/ml for tenofovir.

The study was performed with 54 participants; data generated from a total of 44 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)	4.34 ± 0.97	4.38 ± 1.02	-	-
C_{max} (ng/mL)	2324 ± 763 (2208)	2390 ± 550 (2336)	94.5	87.3 – 102.3
AUC_{0-72h} (ng.h/mL)	55153 ± 21306 (51339)	58346 ± 15917 (56242)	91.3	84.5 – 98.6

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)	1.81 ± 0.87	1.90 ± 0.66	-	-
C_{max} (ng/mL)	1861 ± 396 (1819)	1916 ± 407 (1874)	97.1	91.8 – 102.7
AUC_{0-t} (ng.h/mL)	10678 ± 2503 (10386)	10859 ± 2057 (10653)	97.5	93.0 – 102.2
AUC_{0-inf} (ng.h/mL)	11110 ± 2540 (10828)	11347 ± 2143 (11133)	97.3	93.1 – 101.7

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)	1.18 ± 0.64	1.42 ± 0.60	-	-
C_{max} (ng/mL)	342 ± 82 (332)	354 ± 101 (341)	97.5	91.8 – 103.5
AUC_{0-t} (ng.h/mL)	2165 ± 510 (2103)	2290 ± 652 (2194)	95.9	89.8 – 102.4
AUC_{0-inf} (ng.h/mL)	2578 ± 502 (2527)	2688 ± 664 (2603)	97.1	92.1 – 102.4

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 Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/200/300mg 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.).

4. Summary of product safety and efficacy

[HA553 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, HA553 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 [HA553 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 [HA553 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA553 trade name] has 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, [HA553 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 [HA553 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 [HA553 trade name], manufactured at Strides Shasun Limited KRS Gardens, Tablet Block, 36/7, Suragajakkanahalli Indlavadi Cross, Anekal Taluk, Bangalore – 562 106, India in the list of prequalified medicinal products.