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	[HA551 trade name][*]
Manufacturer of Prequalified Product	Shasun Pharmaceuticals Limited Unit – II, R.S No. 32-34, PIMS Road Periyakalapet, Puducherry India - 605014
Active Pharmaceutical Ingredient(s) (API)	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, (J05AR03)
Therapeutic indication	[HA551 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults and adolescents over 10 years of age and weighing at least 30 kg. [HA551 trade name] may be used in combination with other measures for pre-exposure prophylaxis (PrEP) in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

1. Introduction

[HA551 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults and adolescents over 10 years of age and weighing at least 30 kg.

[HA551 trade name] may be used in combination with other measures for pre-exposure prophylaxis (PrEP) in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

[HA551 trade name] should be prescribed by a physician 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)

Emtricitabine

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

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), polymorphic identity (XPRD), loss on drying, specific optical rotation, residue on ignition, heavy metals, chloride content (potentiometric), organic impurities (HPLC), assay (HPLC), residual solvents, particle size distribution and content of alkyl methane sulfonates (LC/MS/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 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 is a BCS Class 3 API, i.e. of high solubility and low permeability.

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), fumaric acid (HPLC) and of the polymorphic form (XRPD), clarity of solution, water content (KF), heavy metals, melting point (DSC), related compounds (HPLC), enantiomeric impurity (chiral HPLC; ≤ 0.15%), assay and fumaric acid content (HPLC), residual solvents and particle size. 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 XRPD and 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, anhydrous lactose, pregelatinised starch, croscarmellose sodium and magnesium stearate. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains lactose monohydrate, hypromellose, titanium dioxide and triacetin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 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 white to off-white, capsule-shaped film-coated tablet debossed with 'RF14' on one side and plain on the other side. The tablets are packaged in an HDPE bottle with child resistant polypropylene closure with heat seal liner. The bottle also contains a desiccant sachet.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator product, Truvada® film coated tablets. The selection of excipients was based on the qualitative composition of the comparator product, supported by API-API and API-excipient compatibility studies performed on the binary mixtures, using inter alia DSC analyses. The results of the formulation development studies indicate that the manufacturing parameters, process, including optimization of excipients had been satisfactorily studied.

TDF is a high dose, low density API with poor flow properties therefore needs densification to achieve satisfactory flow properties. Due to the sensitivity of the APIs towards hydrolysis a dry granulation process was selected. 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. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average weight, uniformity of dosage units (by content uniformity), water 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 $30^{O}C/75\%RH$ (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 degradation products 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 according to internationally accepted guidelines.

Single dose two-way crossover bioequivalence study of fixed dose combination tablets of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg in healthy, adult, human subjects under fasting condition (study no. 2033/11).

The objective of the study was to compare the bioavailability of the stated emtricitabine/ tenofovir disoproxil fumarate 200/300 mg FDC tablet manufactured by Ranbaxy Laboratories Ltd., India (test drug) with the reference formulation Truvada® (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 emtricitabine/tenofovir disoproxil fumarate 200/300 mg (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 11DT002A.

Treatment R: Reference – 1 tablet Truvada®

(emtricitabine 200 mg +tenofovir disoproxil fumarate 300 mg)

Batch no. 02008554

A 13-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 96 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 emtricitabine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 10 ng/mL for emtricitabine and 5 ng/mL for tenofovir.

The study was performed with 28 participants. Data generated from a total of 27 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.23 ± 0.52	1.24 ± 0.35	_	_
C_{max} (ng/mL)	2732 ± 482 (2693)	2583 ± 367 (2557)	105.2	98.1 – 112.8
AUC_{0-t} (ng h/mL)	12392 ± 1862 (12252)	12267 ± 1918 (12124)	101.1	96.1 – 106.3
AUC_{0-inf} (ng h/mL)	12649 ± 1895 (12507)	12536 ± 1921 (12395)	100.9	96.1 – 106.0

* 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)
tmax (h)	0.92 ± 0.52	0.90 ± 0.43	-	-
Cmax (ng/mL)	376 ± 110 (360)	350 ± 102 (335)	107.1	98.0 – 117.1
AUC0-t (ng·h/mL)	2262 ± 661 (2174)	2188 ± 734 (2079)	104.3	95.9 – 113.5
AUC0-inf (ng·h/mL)	2492 ± 710 (2399)	2427 ± 759 (2317)	103.7	95.5 – 112.6

* geometric mean

**Formerly known as Ranbaxy Laboratories Limited

Conclusions:

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding emtricitabine and tenofovir. Accordingly, the test FDC tablet emtricitabine/tenofovir disoproxil fumarate 200/300 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Truvada® (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA551 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, [HA551 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Truvada® (Gilead Sciences) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA551 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 [HA551 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA551 trade name] has been shown to be bioequivalent with Truvada® 200mg/300 mg tablets (Gilead Sciences Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA551 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 [HA551 trade name] was acceptable for the following indication: **"in combination with other antiretroviral products for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 30 kg and for pre-exposure prophylaxis in certain high-risk populations"**, and would allow inclusion of [HA551 trade name], manufactured at Shasun Pharmaceuticals Limited, Unit-II, R.S No. 32-34, PIMS Road, Periyakalapet, Puducherry India – 605014, in the list of prequalified medicinal products.