## SCIENTIFIC DISCUSSION

**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.**

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|---|---|
| **Name of the Finished Pharmaceutical Product:** | [HA552 trade name][*] |
| **Manufacturer of Prequalified Product:** | Strides Pharma Science Limited<br>KRS Gardens, Tablet Block<br>36/7, Suragajakkanahalli<br>Indlavadi Cross<br>Anekal Taluk<br>Bangalore – 562 106<br>India<br>Tel: 91-80-67840600 |
| **Active Pharmaceutical Ingredients (APIs):** | Emtricitabine, tenofovir disoproxil fumarate |
| **Pharmaco-therapeutic group (ATC Codes):** | Antivirals for treatment of HIV infections, combinations (J05AR03) |
| **Therapeutic indication:** | [HA552 trade name] is indicated in combination with other antiretroviral products for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents from 10 years of age and weighing ≥ 30 kg.<br><br>Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg Tablets may be used for pre-exposure prophylaxis in certain high-risk populations. |

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

## 1. Introduction

[HA552 trade name] is indicated 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. [HA552 trade name] may be used for pre-exposure prophylaxis in certain high-risk populations.

[HA552 trade name] should be prescribed by a physician experienced in the management of HIV infection.

## 2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredients (APIs)

*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*

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, GC), 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 lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch and magnesium stearate. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose / hypromellose, titanium dioxide and polyethylene glycol / macrogol.

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 coloured, film coated, biconvex, capsule shaped tablet, with "TE" engraved on one side and plain on the other side. The tablets are packaged in an HDPE bottle with PP screw closure and containing a silica gel 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. Analysis of the comparator product identified a quality target product profile that included dissolution and other aspects of product quality and equivalence. The selection of the core tablet excipients was based on the qualitative composition of the comparator product, API-API and API-excipient compatibility studies and their suitability to achieve the desired tablet characteristics.

The wet granulation process was selected for manufacture of the core tablets. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. To protect the product from moisture a silica gel desiccant is included in the bottle packs.

*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), disintegration, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), microbial limits and residual solvents. The test methods have been satisfactorily validated.

*Stability testing*

Stability studies have been conducted at 25°C/60%RH (zone II), 30°C/65%RH (zone IVa) and 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. Degradation was observed, noticeably at accelerated, zone IVa and zone IVb conditions. The studies showed that "Do not store above 25ºC" is an appropriate storage condition for the product, with excursions to 30ºC permissible. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusions

The quality part of the dossier is accepted.

## 3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2008 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of [HA552 trade name] of Strides Shasun Limited, India and Truvada® (Emtricitabine 200mg and Tenofovir disoproxil fumarate 300mg) Tablets, of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions (study no. 08-VIN-151).

The objective of the study was to compare the bioavailability of the stated [HA552 trade name] manufactured by Strides Shasun Limited, 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 [HA552 trade name]
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 7206150.

Treatment R: Reference – 1 tablet Truvada®
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. C710245A.

A 12 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 emtricitabine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 15 ng/ml for emtricitabine and 4 ng/ml for tenofovir.

The study was performed with 44 participants; data generated from a total of 39 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 (*) | Reference (R) arithmetic mean ± SD (*) | log-transformed parameters | |
|---|---|---|---|---|
| | | | Ratio T/R (%) | Conventional 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 1.51 ± 0.62 | 1.69 ± 0.70 | - | - |
| $C_{max}$ (ng/ml) | 2445 ± 654 (2364) | 2488 ± 594 (2411) | 98.1 | 93.2 – 103.2 |
| $AUC_{0-t}$ (ng.h/ml) | 12082 ± 2149 (11929) | 12288 ± 2019 (12106) | 98.5 | 96.0 – 101.2 |
| $AUC_{0-inf}$ (ng.h/ml) | 12432 ± 2133 (12286) | 12636 ± 1989 (12462) | 98.6 | 96.2 – 101.0 |

* 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) |
| $t_{max}$ (h) | 1.09 ± 0.55 | 1.09 ± 0.52 | - | - |
| $C_{max}$ (ng/ml) | 336 ± 100 (323) | 335 ± 93 (323) | 99.9 | 92.2 – 108.3 |
| $AUC_{0-t}$ (ng.h/ml) | 2326 ± 537 (2274) | 2353 ± 643 (2274) | 100.0 | 95.1 – 105.2 |
| $AUC_{0-inf}$ (ng.h/ml) | 2511 ± 531 (2468) | 2563 ± 648 (2491) | 99.0 | 94.7 – 103.6 |

* geometric mean

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 [HA552 trade name] 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

[HA552 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability, [HA552 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Truvada® for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [HA552 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA552 trade name] has shown to be bioequivalent with Truvada® (Gilead Sciences Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA552 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [HA552 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) infected adults and adolescents from 10 years of age and weighing at least 30 kg**" and has advised that the quality, efficacy and safety of [HA552 trade name] allow inclusion of [HA552 trade name], manufactured at Strides Shasun Ltd, KRS Gardens Tablet Block 36/7, Suragajakkanahalli Indlavadi Cross, Anekal Taluk, Bangalore – 562 106 India, in the list of prequalified medicinal products.