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	[HA535 trade name]*
Manufacturer of Prequalified Product	Strides Shasun Limited Oral solid dosage forms division Tablet Block 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk, Bangalore - 560 106, INDIA
Active Pharmaceutical Ingredient(s) (API)	Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07).
Therapeutic indication	[HA535 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg. [HA535 trade name] may be used for pre-exposure prophylaxis (PrEP) as an additional prevention choice for adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection as part of combination prevention approaches. [HA535 trade name] is indicated for the treatment of chronic hepatitis B in adults with: • compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. • evidence of lamivudine-resistant hepatitis B virus. • decompensated liver disease. [HA535 trade name] is indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age and weighing ≥ 35 kg with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
† Formerly Strides Shasun Limited.

1. Introduction

[HA535 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infection and chronic hepatitis B (see part 4 for full indications).

[HA535 trade name] should be prescribed by a physician experienced in the management of HIV infection or hepatitis B.

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)

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 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 and polymorphic form, water content, heavy metals, sulphated as, fumaric acid content, related substances (HPLC and GC), assay (HPLC), S-isomer content (≤ 1.0% by chiral HPLC), residual solvents, particle size and foreign matter. The specifications control potential mutagenic impurities 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 croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, pregelatinised starch and magnesium stearate. Magnesium stearate is obtained from vegetable origin. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide and polyethylene glycol.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 300mg TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir. The tablet is white, circular, film-coated and convex, engraved TDF on one side and plain on the other side. The tablets are presented in Al/Al cold form blisters and in white opaque HDPE bottles, with white opaque screw cap with induction sealed liner and containing a silica gel sachet as desiccant.

The composition of the multisource product is qualitatively similar to that of the comparator product, Viread®. Wet granulation, justified by the physico-chemical properties of the API and the flow properties of the powder, has been selected for the manufacture of the core tablets. After compression, the core tablets are coated with a proprietary coating mixture.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented demonstrated the consistency of the process and the quality of the product. The biobatch showed dissolution profiles similar to that of the comparator product.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification (HPLC and UV), average weight, uniformity of weight, uniformity of dosage units (by weight variation), tablet dimensions, disintegration time, water content, dissolution, residual solvents, related substances (HPLC), assay (HPLC) and microbial limits. The test methods have been satisfactorily described and 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 conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed an increase of degradation products with time at all storage conditions in both pack types, though within agreed 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 2008 according to internationally accepted guidelines:

Open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study of [HA535 trade name] of Strides Arcolab Limited, India and Reference product Viread® (tenofovir disoproxil fumarate) tablets, 300mg of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions (study no. 07-VIN-150).

The objective of the study was to compare the bioavailability of the stated [HA535 trade name] tablet manufactured by Strides Arcolab Limited, India (test drug) with the same dose of the reference formulation (Viread®, 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 [HA535 trade name]
(tenofovir disoproxil fumarate 300 mg)
Batch no. 7203834.

Treatment R: Reference – 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. FDB056A.

A 9-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 96 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 tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 3 ng/ml for tenofovir.

The study was performed with 52 participants; data generated from a total of 50 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.00 ± 0.42	0.89 ± 0.45	–	–
C_{max} (µg/mL)	287 ± 78 (278)	301 ± 73 (294)	94.7	90.2 – 99.5
AUC_{0-t} (µg·h/mL)	2095 ± 594 (2030)	2144 ± 538 (2092)	97.0	92.7 – 101.6
AUC_{0-inf} (µg·h/mL)	2253 ± 647 (2183)	2277 ± 535 (2229)	98.0	93.8 – 102.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding tenofovir. Accordingly, the test tablet of [HA535 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Viread® (Gilead Sciences).

4. Summary of product safety and efficacy

[HA535 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, [HA535 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Viread® (Gilead Sciences) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA535 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 [HA535 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA535 trade name] has been shown to be bioequivalent with Viread® (Gilead Sciences, Inc. USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA535 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 [HA535 trade name] was acceptable for the following indication: 'treatment of HIV infection and treatment of chronic hepatitis B', and would allow inclusion of [HA535 trade name], manufactured at Strides Shasun Limited, Oral solid dosage forms division, Tablet Block, 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk, Bangalore - 560 106, India in the list of prequalified medicinal products.