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:	[HA525 trade name] *
Manufacturer of Prequalified Product:	Shasun Pharmaceutical Limited Unit-II, R.S. NO.:32, 33 & 34 Shasun Road, Periyakalapet Puducherry 605 014 India
Active Pharmaceutical Ingredients (APIs):	Lamivudine + Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors (lamivudine: J05AF05; tenofovir: J05AF07)
Therapeutic indication:	[HA525 trade name] is indicated in combination with at least one other antiretroviral for the treatment of HIV-1 infection in adults and adolescents aged over 12 years

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

[1] Formerly Ranbaxy Labs Limited

1. Introduction

[HA525 trade name] (Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg Tablets) is indicated in combination with at least one other antiretroviral medicine for the treatment of HIV-1 infection adults and adolescents aged over 12 years.

[HA525 trade name] should be prescribed on the advice of 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 Ingredient (API)

Lamivudine

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus highly soluble over the pH range 1 to 6.8.

Lamivudine, which is described in the Ph.Int., Ph.Eur. and the USP, is considered well-established in the WHO Prequalification Programme. The specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), light absorption, water, limit of lamivudine enantiomer (chiral HPLC, ≤ 0.3%), chromatographic purity (HPLC), assay (HPLC), bulk density (tapped and untapped), particle size and residual solvents (GC).

Stability was tested 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 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.

Tenofovir disoproxil fumarate, (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 tenofovir disoproxil fumarate were confirmed by the route of synthesis and spectrometric data.

The specifications for tenofovir disoproxil fumarate include tests for description, solubility, identification of the API and fumaric acid and of the polymorphic form (XRPD), clarity of solution, water content, heavy metals, melting point (DSC), related compounds (HPLC), enantiomeric impurity (≤ 0.15%; chiral HPLC), 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 ≤ 5.0 ppm. This is in accordance with the requirement of Tenofovir Disoproxil Fumarate Ph.Int.

Tenofovir disoproxil fumarate is known to exhibit polymorphism and exists in two forms, namely a low-melting form (m.p. 112-114°C) and a high-melting form (m.p. 114-118°C). The high melting form, controlled by XRPD and melting point, is consistently produced. The test methods have been adequately validated.

Stability was tested 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, magnesium stearate and microcrystalline cellulose. Magnesium stearate is obtained from vegetable origin. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide and triacetin.

Finished pharmaceutical product (FPP)

Each tablet contains 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

[HA525 trade name] are white to off-white, oval-shaped, film-coated tablets debossed with 'RH80' on one side and plain on the other. The tablets are presented in an HDPE bottle with child-resistant screw cap. The bottle also contains a silica gel desiccant sachet to protect the tablets from moisture.

Pharmaceutical development and manufacture

The development of the final composition of the multi-source product has been described. The objective was to develop an immediate-release, stable, fixed-dose combination tablet bioequivalent to the comparator products, Viread® 245 mg film-coated tablets (containing 300 mg tenofovir disoproxil fumarate) and Epivir® 300 mg film-coated tablets taken concomitantly. The excipients selected for the core tablets are commonly used in tablets and are present in the individual comparator products; the selection was furthermore supported by API-excipient compatibility studies.

Tenofovir disoproxil fumarate is highly sensitive to moisture, undergoing hydrolysis, thus it was decided to process tenofovir disoproxil fumarate using a dry granulation process. Lamivudine, being a dense and free-flowing material, is introduced extragranularly. After compression the core tablets are coated with an aqueous proprietary coating mixture. The process parameters were optimised to obtain tablets of desired characteristics, targeting the dissolution profiles of the innovator products. The multi-source product and the comparator products showed very rapid dissolution characteristics. Satisfactory in-process controls have been established. Validation data demonstrated the consistency of the process and the quality of the product.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the APIs and the colorant, 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 described and 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 an increase of degradation products of tenofovir disoproxil fumarate with time, though within agreed limits. 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 2010 according to internationally accepted guidelines.

A randomised, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, pivotal bioequivalence study comparing fixed-dose combination tablets of Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg manufactured by Shasun Pharmaceuticals Limited (Formerly known as Shasun Chemical and Drugs Ltd.), India, manufactured for Ranbaxy Laboratories Limited,

India with Epivir® (Lamivudine) 300 mg tablets of GlaxoSmithKline, USA co-administered with Viread® (Tenofovir Disoproxil Fumarate) 300 mg tablets of Gilead Sciences, Inc., USA in 36 healthy human adult male subjects, under fasting conditions (study No. 085-10).

The objective of the study was to compare the bioavailability of the stated Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg fixed-dose combination tablet manufactured by Shasun Pharmaceuticals Limited, India (test drug) with the same dose of the individual reference formulations (Epivir®, GlaxoSmithKline, and Viread®, Gilead Sciences) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, 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 Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg (lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 10DN01A

Treatment R: Reference – 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 9L001.
Reference – 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 02006891

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 lamivudine and tenofovir were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 15 ng/mL for lamivudine and about 10 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 34 subjects were used for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Lamivudine

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} (hour)	1.37 ± 0.73	1.27 ± 0.53	–	–
C_{max} (ng/mL)	3289 ± 952 (3164)	3472 ± 999 (3320)	95.3	89.2–101.8
AUC_{0-t} (ng·hour/mL)	14610 ± 3241 (14266)	14714 ± 3480 (14325)	99.6	95.7–103.6
AUC_{0-inf} (ng·hour/mL)	14936 ± 3246 (14598)	15046 ± 3490 (14663)	99.6	95.8–103.5
* 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} (hour)	1.07 ± 0.50	1.02 ± 0.34	–	–
C_{max} (ng/mL)	305 ± 71 (297)	300 ± 81 (290)	102.6	96.2–109.5
AUC_{0-t} (ng·hour/mL)	2229 ± 585 (2156)	2279 ± 606 (2197)	98.1	93.7–102.7
AUC_{0-inf} (ng·hour/mL)	2700 ± 625 (2635)	2757 ± 649 (2677)	98.0	93.5–102.8
* 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 lamivudine and tenofovir. Accordingly, the test Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg fixed-dose combination tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences).

4. Summary of Product Safety and Efficacy

[HA525 trade name] conforms to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to and thus interchangeable with the innovator products, Epivir® (lamivudine 300 mg) and Viread® (tenofovir disoproxil fumarate 300 mg) for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of this product is considered acceptable when guidance and restrictions in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA525 trade name] (Ranbaxy labs Ltd, India) has been shown to be bioequivalent to Epivir® 300 mg tablets (GlaxoSmithKline, USA) and Viread® 300 mg tablets (Gilead Sciences, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA525 trade name] is considered effective and safe when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit–risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA525 trade name] was acceptable for the following indications: in combination with at least one other antiretroviral medicine for the treatment of HIV-1 infection in adults and adolescents aged over 12 years, and has advised inclusion of [HA525 trade name], manufactured at Shasun Pharmaceutical Limited, Puducherry, India, in the list of prequalified medicinal products.