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	[HA729 trade name][*]
Manufacturer of Prequalified Product	Strides Pharma Science Limited, KRS Gardens, Tablet Block, 36/7, Suragajakkanahalli, Indlavadi cross Anekal Taluk, Bangalore Karnataka, 562 106 India
Active Pharmaceutical Ingredients (APIs)	Dolutegravir (as sodium)/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group **(ATC Code)**	Antivirals for treatment of HIV infections, combinations, (J05AR)
Therapeutic indication	[HA729 trade name] is indicated for the treatment of human immunodeficiency virus-Type 1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA729 trade name] is indicated for indicated for the treatment of HIV-1 infection in adults and adolescents weighing at least 30 kg, in combination with other antiretroviral medicinal products.

[HA729 trade name] should be prescribed by a health care provider experienced in the management of tuberculosis 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 Ingredients (APIs)

Dolutegravir sodium, lamivudine and tenofovir disoproxil fumarate have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [HA729 trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two

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

components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate, crospovidone, povidone, lactose monohydrate, croscarmellose sodium, pregelatinized starch, colloidal silicon dioxide, magnesium stearate, mannitol and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol and talc. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, capsule-shaped, biconvex, film-coated tablet, debossed with 'TLD' on one side and with a break line on the other side. The break line is to facilitate breakage for ease of swallowing. The tablets are presented in white, opaque HDPE bottles and closed with polypropylene ribbed screw caps with heat seal liner. Each bottle also contains a 3g molecular sieve canister as desiccant.

The aim of the development was to formulate an immediate release FDC dosage form, which is stable, and bioequivalent to the individual WHO comparator products Tivicay® (Dolutegravir 50 mg) Tablets, Epivir® (Lamivudine 300 mg) Tablets and Viread® (Tenofovir disoproxil fumarate 300 mg) Tablets. The excipients were selected based on the excipients used in the comparator products, and API-excipient compatibility studies. From API-API compatibility studies, significant level of impurity had been observed between tenofovir disoproxil fumarate and dolutegravir API. Hence, the FDC tablet has been designed as a bilayer formulation, having tenofovir disoproxil fumarate – lamivudine in the first layer and dolutegravir in the second layer. Various approaches were adopted for developing the bilayered prototype formulation, upon which the wet granulation manufacturing process was finalised. Based on the satisfactory data of optimization trials, the formulation was finalized, resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of the APIs (UHPLC, retention times and PDA detection), water content (KF), dissolution (UHPLC detection), related substances (HPLC), uniformity of dosage units (by content uniformity), assay (UHPLC), residual solvents and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data showed some degradation for the water sensitive tenofovir disoproxil fumarate, though no significant change was observed and the results for all parameters at the storage conditions were within agreed acceptance criteria. Based on the available stability data, the proposed shelf-life and storage conditions of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle of pack size of 90 tablets is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2018 according to internationally accepted guidelines:

Bioequivalence study of fixed dose combination of Tenofovir Disoproxil Fumarate 300mg + Lamivudine 300 mg + Dolutegravir 50mg tablets in normal, healthy, adult, human subjects under fasting condition (study no. BE/17/138).

The objective of the study was to compare the bioavailability of the stated Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir 300 mg/300 mg/50 mg FDC tablet manufactured by/for Strides Pharma Science Limited, India (test drug) with the reference formulations Viread® (Gilead Sciences, Inc.), Epivir® (GlaxoSmithKline) and Tivicay® (GlaxoSmithKline) 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 [HA729 trade name]
(tenofovir disoproxil fumarate 300 mg + lamivudine 300 mg + dolutegravir 50 mg)
Batch no. 7231777

Treatment R: Reference
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg)
Batch no. 008557.
– 1 tablet Epivir® (lamivudine 300 mg)
Batch no. 6ZP7456
– 1 tablet Tivicay® (dolutegravir 50 mg)
Batch no. 7ZP3725

A 13 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 27 samples within 72 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC and C_{max} for bioequivalence evaluation. Drug concentrations for tenofovir, lamivudine and dolutegravir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 4 ng/mL for tenofovir, 20 ng/mL for lamivudine and 28 ng/mL for dolutegravir.

The study was performed with 72 participants; data generated from a total of 69 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.
Arithmetic mean and geometric mean values of the pharmacokinetic variables for tenofovir, lamivudine and dolutegravir 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)	1.16 ± 0.67	0.97 ± 0.41	-	-
C_{max} (ng/mL)	397 ± 117 (380)	403 ± 118 (384)	99.1	92.8 – 105.7
AUC_{0-t} (ng·h/mL)	2625 ± 656 (2544)	2657 ± 680 (2571)	99.0	95.1 – 103.0
AUC_{0-inf} (ng·h/mL)	2813 ± 683 (2731)	2868 ± 731 (2777)	98.3	94.7 – 102.2

Lamivudine

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)[#]	2.16 ± 0.81	1.71 ± 0.78	-	-
C_{max} (ng/mL)	2657 ± 587 (2592)	2618 ± 643 (2539)	102.1	97.8 – 106.6
AUC_{0-t} (ng·h/mL)	13964 ± 2868 (13683)	13714 ± 3128 (13372)	102.3	98.6 – 106.1
AUC_{0-inf} (ng·h/mL)	14266 ± 2872 (13989)	14036 ± 3109 (13707)	102.1	98.5 – 105.7

Dolutegravir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	90% CI (ANOVAlog)
t_{max} (h)	2.89 ± 1.99	2.69 ± 1.84	-	-
C_{max} (ng/mL)	3470 ± 926 (3355)	3774 ± 1178 (3602)	93.1	87.0 – 99.7
AUC_{0-t} (ng·h/mL)	67261 ± 17336 (65047)	70678 ± 20082 (67807)	95.9	91.3 – 100.8
AUC_{0-inf} (ng·h/mL)	70789 ± 18887 (68282)	74438 ± 21737 (71245)	95.8	91.3 – 100.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding tenofovir, lamivudine and dolutegravir. Accordingly, the test [HA729 trade name] tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Viread® (Gilead Sciences, Inc.), Epivir® (GlaxoSmithKline) and Tivicay® (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA729 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator products. According to the submitted data on quality and bioavailability, [HA729 trade name] is pharmaceutically and

therapeutically equivalent and thus interchangeable with the WHO-recommended comparator products Epivir®, Viread® and Tivicay®, for which benefits have been proven in terms of clinical 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 [HA729 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA729 trade name] has shown to be bioequivalent with Epivir® (GlaxoSmithKline), Viread® (Gilead Sciences, Inc.) and Tivicay® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA729 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 [HA729 trade name] was acceptable for the following indication: 'the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg' and has advised that the quality, efficacy and safety of [HA729 trade name] allow inclusion of [HA729 trade name], manufactured at Strides Pharma Science Limited, , KRS Gardens, Tablet Block, 36/7, Suragajakkanahalli, Indlavadi Cross, Anekal Taluk, Bangalore, Karnataka, 562 106, India, in the list of prequalified medicinal products.