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	[HA679 trade name][*]
Manufacturer of Prequalified Product	Laurus Labs Limited Plot No. 19, 20 & 21, Western Sector APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011 Andhra Pradesh 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	[HA679 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. [HA679 trade name] may be used for pre-exposure prophyaxis (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. [HA679 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. [HA679 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.

1. Introduction

[HA679 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).

[HA679 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. Solubility data demonstrated that TDF is highly soluble in aqueous medium over the pH range 1.0 – 6.8.

TDF has 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 API, used in the manufacture of Tenofovir Disoproxil Fumarate 300mg Tablets, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium and magnesium stearate, all being pharmacopoeial controlled. Magnesium stearate is from plant origin. A TSE / BSE free attestation has been provided for lactose monohydrate. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, triacetin and FD&C Blue #2/ Indigo carmine.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 300 mg of Tenofovir disoproxil fumarate, equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

The multisource product is a blue coloured, oval shaped, film-coated tablet, with "LA16" debossed on one side and plain on the other side. The tablets are packaged in HDPE bottles with silica gel canisters and polyester coil closed with polypropylene child resistant closures. The HDPE bottles may be packed in a mono carton or many HDPE bottles may be packed in a shipper.

The aim of the development programme was to formulate an immediate-release tablet, which is essentially similar to the WHO comparator product, Viread ® 300 mg film-coated tablets. Based on the results of excipient compatibility studies, excipients identical to the WHO comparator product were selected for the multisource product. Process development focused on the critical quality attributes that could be impacted by a realistic change to the drug product formulation or manufacturing process. Wet granulation was considered to be suitable for the manufacture of the core tablets. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and colorants, water content (KF), uniformity of dosage units (by weight variation), dissolution (UV 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°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed all parameters were well within the agreed limits at both storage conditions. 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 2016 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of Tenofovir disoproxil fumarate tablets 300 mg of Laurus Labs, India and Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc., USA in healthy, adult, human subjects under fasting condition (study no. 14-VIN-322).

The objective of the study was to compare the bioavailability of the stated Tenofovir disoproxil fumarate 300 mg tablet manufactured by/for Laurus Labs, India (test drug) with the reference formulation Viread® (Gilead Sciences, Inc.) 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 Tenofovir disoproxil fumarate 300 mg
(tenofovir disoproxil fumarate 300 mg)
Batch no. ATDF100315

Treatment R: Reference – 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 002706

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 5 ng/ml for tenofovir.

The study was performed with 36 participants; data generated from a total of 31 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 table:

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)	0.67 (0.33 – 1.25)	0.67 (0.35 – 2.0)	–	–
C_{max} (ng/mL)	433 ± 112 (420)	412 ± 93 (402)	104.5	96.8 – 112.8
AUC_{0-t} (ng·h/mL)	3063 ± 653 (2981)	2884 ± 639 (2809)	106.1	98.5 – 114.3
AUC_{0-inf} (ng·h/mL)	3278 ± 651 (3205)	3106 ± 673 (3029)	105.8	98.8 – 113.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding tenofovir. Accordingly, the test [HA679 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, Inc.).

4. Summary of product safety and efficacy

[HA679 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, [HA679 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 [HA679 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 [HA679 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA679 trade name] has been shown to be bioequivalent with Viread® (Gilead Sciences, Inc. USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA679 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 [HA679 trade name] was acceptable for the following indication: 'treatment of HIV infection" and "treatment of chronic hepatitis B', and would allow inclusion of [HA679 trade name], manufactured at Laurus Labs Limited, Plot No. 19, 20 & 21,

Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India, in the list of prequalified medicinal products.