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:	[HA516 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block A, Module-IV Plot No. 2209, GIDC Industrial Estate At & Post Sarigam Umbergeon Valsad 396 155 Gujarat India
Active Pharmaceutical Ingredients (APIs):	Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07).
Therapeutic indication:	[HA516 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults and adolescents aged over 12 years. Tenofovir Disoproxil Fumarate 300 mg Tablets is indicated for the treatment of chronic hepatitis B in adults and adolescents aged over 12 years with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation or fibrosis.

1. Introduction

[HA516 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults and adolescents aged over 12 years.

[HA516 trade name] is indicated for the treatment of chronic hepatitis B in adults and adolescents aged over 12 years with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

2. Assessment of Quality

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

Active Pharmaceutical Ingredient (API)

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 prodrug has

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

increased oral bioavailability compared to tenofovir. Tenofovir disoproxil fumarate is a BCS Class 3 API, i.e. of high solubility and low permeability.

Tenofovir 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, fumaric acid and of the polymorphic form (XRPD), melting range, water content, heavy metals, sulphated ash, fumaric acid content, related substances (HPLC), assay (HPLC), enantiomeric purity (S-isomer ≤ 0.2%), residual solvents and particle size. 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.

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, magnesium stearate, microcrystalline cellulose and pregelatinised starch. The commercially sourced proprietary film-coating mixture contains FD & C Blue # 2 (indigo carmine aluminium lake), hypromellose, lactose monohydrate, titanium dioxide and triacetin.

Finished Pharmaceutical Product (FPP)

Each tablet contains 300 mg tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir. The tablet is blue-coloured, oval-shaped, biconvex, film-coated and debossed 'CL 77' on one side and plain on other side. The tablets are presented in an HDPE bottle with child-resistant screw cap. The bottle also contains a silica gel sachet.

Pharmaceutical development and manufacture

The development of the final composition of the multisource product has been described. The objective was to develop a stable, immediate-release tablet bioequivalent to the comparator product, Viread®. The excipients selected for the core tablets are commonly used in tablets and are qualitatively similar to that of the comparator product and are supported by API-excipient compatibility studies. The quality target product profile included dissolution, targeting the profiles of the comparator product.

Since tenofovir disoproxil fumarate was observed to have poor flow properties, wet granulation was selected for the manufacture of the core tablets. After compression, the core tablets are coated with a proprietary coating mixture. The process parameters were optimised to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the API and the colorants, average weight, disintegration time, loss on drying, dissolution, uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), microbial enumeration and specified microorganisms. 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 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 2011 according to internationally accepted guidelines.

Bioequivalence study of single-dose [HA516 trade name] tablets (each tablet contains 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil) manufactured by Macleods Pharmaceuticals Ltd, India in comparison with Viread® (tenofovir disoproxil fumarate) tablets 300 mg (each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil) manufactured for Gilead Sciences Inc, USA in healthy adult subjects under fasting condition (study No. BEQ-512-TENO-2010).

The objective of the study was to compare the bioavailability of the stated [HA516 trade name] manufactured by Macleods Pharmaceuticals Ltd, 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, randomised, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T:	Test – 1 tablet [HA516 trade name] (tenofovir disoproxil fumarate 300 mg) Batch No. ETA3001A.
Treatment R:	Reference – 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch No. XBF.

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 72 hours after the 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 analysed 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 28 participants; data generated from a total of 27 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	0.94 ± 0.31	0.99 ± 0.35	–	–
C_{max} (ng/ml)	298 ± 54 (294)	296 ± 85 (285)	103.1	96.1–110.5
AUC_{0-t} (ng·hour/ml)	2103 ± 513 (2044)	2027 ± 474 (1977)	103.4	97.8–109.3
AUC_{0-inf} (ng·hour/ml)	2315 ± 502 (2262)	2247 ± 487 (2198)	102.9	98.1–108.0

* geometric mean

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 [HA516 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

[HA516 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 [HA516 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Viread® 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 considered. 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 [HA516 trade name] is used in accordance with the conditions as stated in the SPC.

Bioequivalence

[HA516 trade name] has shown to be bioequivalent with Viread® (Gilead Sciences, Inc. USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA516 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA516 trade name] was acceptable for the following indications: "treatment of HIV-1 infected adults and adolescents aged over 12 years in combination with other antiretroviral medicinal products" and "treatment of chronic hepatitis B in adults and adolescents aged over 12 years with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation or fibrosis", and has advised that the quality, efficacy and safety of [HA516 trade name] are acceptable to allow inclusion of [HA516 trade name], manufactured at Macleods Pharmaceuticals Ltd, Valsad, Gujarat, India, in the list of prequalified medicinal products.