This part outlines the scientific assessment and knowledge about this product available 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:	[HA561 trade name]*
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Phase II and Phase III, Unit II, Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210, India
Active Pharmaceutical Ingredients (APIs):	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Codes):	Antivirals for treatment of HIV infections, combinations (emtricitabine and tenofovir disoproxil: J05AR03)
Therapeutic indication:	[HA561 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents from 10 years of age and weighing ≥ 30 kg. [HA561 trade name] may be used for pre-exposure prophylaxis in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

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

1. Introduction

[HA561 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing ≥ 30 kg. [HA561 trade name] may be used for pre-exposure prophylaxis in certain high-risk populations.

[HA561 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

2. Assessment of Quality

Active pharmaceutical Ingredients (APIs)

Emtricitabine

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified emtricitabine (up to 200 mg oral dose) as a BCS class 1 API. Emtricitabine is thus highly soluble according to the BCS.

Emtricitabine, 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone, has two chiral centres. The desired stereochemistry is built into the key intermediate in the multi-step synthesis of emtricitabine. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications include tests for description, solubility, identification, loss on drying, sulfated ash, heavy metals, enantiomer/epimer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents, particle size, polymorphic identity and boron content.

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 packing material.

Tenofovir disoproxil fumarate (TDF)

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 a BCS high solubility.

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, of fumaric acid and of the polymorphic form (XRPD), melting range, water content, heavy metals, residue on ignition, fumaric acid content, related substances (HPLC), assay (HPLC), enantiomeric purity (S-isomer ≤ 0.2%), residual solvents, particle size and bulk density. 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 lactose monohydrate, microcrystalline cellulose, pre-gelatinized starch, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The commercially sourced proprietary film-coating mixture contains lactose monohydrate,

hypromellose, titanium dioxide, triacetin, FD&C Blue #2 / indigo carmine aluminium lake. Assurance by means of certificates was provided that the excipients are BSE/TSE free.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 200 mg of emtricitabine and 300 mg of TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

The multisource product is a blue-coloured, capsule-shaped, biconvex, film-coated tablet debossed "L 24" on one side of the tablet and plain on other surface. The tablets are presented in an HDPE bottle, also containing a silica gel sachet, and in Alu-Alu blisters.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator product, Truvada®. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information of the qualitative composition of the comparator product and compatibility with the APIs. Characterization of the comparator product identified a quality target product profile, including dissolution and other product attributes.

The dry granulation process, using roll compactor, was selected to manufacture the granules. The composition and process parameters were optimised to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average weight, disintegration time, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC) and microbiological examination. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH and 25°C/60%RH as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was observed, though the related substances content remained within acceptable 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 2011 according to internationally accepted guidelines:

Bioequivalence study of single dose of [HA561 trade name] (each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets (each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil) manufactured for Gilead Sciences, Inc., USA in healthy, adult, human subjects under fasting condition (study no. BEQ-515-ET(F)-2010).

The objective of the study was to compare the bioavailability of the stated [HA561 trade name] tablet manufactured by Macleods Pharmaceuticals Limited, India (test drug) with the same dose of the reference formulation (Truvada®, Gilead Sciences Inc.) 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 [HA561 trade name]
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. EEA2101A.

Treatment R: Reference – 1 tablet Truvada®
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 02008349.

A 9 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 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 emtricitabine and tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for emtricitabine and 5 ng/ml for tenofovir.

The study was performed with 30 participants; data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Emtricitabine

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} (h)	1.69 ± 0.91	1.59 ± 0.67	-	-
C_{max} (ng/ml)	2427 ± 662 (2343)	2377 ± 679 (2293)	102.2	93.8 – 111.3
AUC_{0-t} (ng.h/ml)	11417 ± 2458 (11146)	11181 ± 2529 (10917)	102.1	95.7 – 108.9
AUC_{0-inf} (ng.h/ml)	11889 ± 2422 (11630)	11634 ± 2496 (11388)	102.1	96.2 – 108.4

* 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} (h)	1.33 ± 0.58	0.99 ± 0.35	-	-
C_{max} (ng/ml)	287 ± 97 (268)	300 ± 84 (288)	93.1	84.9 – 102.2
AUC_{0-t} (ng.h/ml)	2006 ± 776 (1855)	1947 ± 597 (1868)	99.3	91.0 – 108.4
AUC_{0-inf} (ng.h/ml)	2229 ± 793 (2090)	2194 ± 620 (2115)	98.8	90.9 – 107.4

* 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 emtricitabine and tenofovir. Accordingly, the test fixed dose combination tablet [HA561 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Truvada® (Gilead Sciences Inc.).

4. Summary of Product Safety and Efficacy

[HA561 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 [HA561 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Truvada® (emtricitabine 200 mg + 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 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 [HA561 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA561 trade name] has shown to be bioequivalent with Truvada® 200 mg/300 mg tablets (Gilead Sciences Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA561 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 [HA561 trade name] was acceptable for the following indication: **"treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents (from 10 years of age and weighing≥ 30 kg)"** and has advised that the quality, efficacy and safety of [HA561 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II/Phase III Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India, in the list of prequalified medicinal products.