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	[HA459 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Plot No. 25–27 Survey No. 366, Premier Industrial Estate Kachigam, Daman 396 320 India
Active Pharmaceutical Ingredients (APIs)	Lamivudine and zidovudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR01)
Therapeutic indication	Treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

[HA459 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA459 trade name] should not be used for patients with clinically significant hypersensitivity to lamivudine, zidovudine, or to any of the components contained in the formulation. It is recommended that therapy is given only on the advice of a health care provider experienced in the management of HIV 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 Ingredient (API)

Lamivudine and zidovudine are both class 1 APIs according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*).

Lamivudine and zidovudine are thus highly soluble according to the BCS.

Lamivudine and zidovudine are described in the Ph.Int., Ph.Eur. and USP, and are considered well-established in the Prequalification Programme. The APIs are adequately controlled by their respective

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

quality specifications which are pharmacopoeial based, with additional in-house specifications including particle size and bulk density for both APIs.

Stability testing was conducted according to the requirements of WHO. The proposed re-test periods are justified based on the stability results when the APIs are stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is obtained from vegetable origin. The film coating contains hypromellose, macrogol (polyethylene glycol) 400, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

[HA459 trade name] are white, biconvex, modified capsule- shaped, film-coated tablets having a score on one side and 'ML 6' debossed on the other side. The score line is intended for subdivision of tablets when the tablet is to be administered as half a dose, as supported by divisibility studies. The tablets are packaged in a HDPE container with pack insert and 1 g pillow pack containing an adsorbent and finally induction sealed or in white opaque PVC/PVdC-aluminium blister cards**.**

Pharmaceutical development and manufacture

The development of the final composition of [HA459 trade name] has been described. The objective was to develop a stable product, bioequivalent to the comparator product Combivir®. Analysis of the comparator product identified a target product profile that included the qualitative tablet composition and dissolution profiles.

Since the APIs show poor flow properties, the wet granulation process was selected for the manufacture of the core tablets. The critical steps of the manufacturing process were optimised and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three batches demonstrated the consistency of the process and the quality of the product.

Specifications

The finished product specifications include appropriate tests for description, identification of the APIs (HPLC and TLC) and titanium dioxide, average weight, disintegration time, water content, dissolution, uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), microbial enumeration test and test for specified microorganisms.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/70%RH as long-term storage conditions and for six months at accelerated conditions. The data showed little change with time and were well within the agreed specifications at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

Bioequivalence study of fixed dose combination of lamivudine 150 mg and zidovudine 300 mg tablets (each tablet contains lamivudine 150 mg and zidovudine 300 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Combivir® (lamivudine 150 mg, zidovudine 300 mg) tablets (each tablet contains lamivudine 150 mg, zidovudine 300 mg) of GlaxoSmithKline, Research

Triangle Park NC27709 in healthy, adult, human subjects under fasting conditions (study no. BEQ-122-LZ (F)-2007).

The objective of the study was to compare the bioavailability of the stated lamivudine/zidovudine 150/300 mg tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference formulation (Combivir® 150/300 mg tablet, GlaxoSmithKline) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, two-treatment, four-period, replicate 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 – lamivudine/zidovudine 150/300 mg tablet
(Lamivudine 150 mg + zidovudine 300 mg)
Batch no. LJ702.

Treatment R: Reference – Combivir® tablet
(Lamivudine 150 mg + zidovudine 300 mg)
Batch no. 6ZP7655.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 24 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 zidovudine were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/ mL for lamivudine and zidovudine.

The study was performed with 36 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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} (h)	1.3 ± 0.6	1.2 ± 0.6	-	-
C_{max} (ng/ mL)	1746 ± 504 (1680)	1679 ± 400 (1632)	102.9	96.3 – 110.0
AUC_{0-t} (ng.h/ mL)	6634 ± 1548 (6468)	6465 ± 1539 (6296)	102.7	98.6 – 107.1
AUC_{0-inf} (ng·h/ mL)	6810 ± 1576 (6644)	6645 ± 1561 (6476)	102.6	98.6 – 106.8

* geometric mean

Zidovudine

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)	0.5 ± 0.3	0.6 ± 0.4	-	-
C_{max} (ng/ mL)	021 ± 2068 (2548)	2992 ± 1901 (2562)	99.4	84.8 – 116.6
AUC_{0-t} (ng.h/ mL)	2797 ± 701 (2715)	2789 ± 693 (2705)	100.4	96.1 – 104.9
AUC_{0-inf} (ng.h/ mL)	2857 ± 708 (2774)	2847 ± 696 (2763)	100.4	96.1 – 104.8

* geometric mean

The results of the study show that pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine and zidovudine. Accordingly, the test lamivudine/zidovudine 150/300 mg tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Combivir® (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA459 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, [HA459 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Combivir® (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA459 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 [HA459 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA459 trade name] has been shown to be bioequivalent with Combivir® (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA459 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 [HA459 trade name] was acceptable for the following indication: treatment of HIV-1 infection in combination with one more other antiretroviral agents', and would allow inclusion of [HA459 trade name], manufactured at Macleods Pharmaceuticals Limited, Daman (U.T.), India in the list of prequalified medicinal products.