This part reflects 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:	[HA629 trade name]*
Manufacturer of Prequalified Product:	Micro Labs Limited Plot No: S-155 to S-159 & N1, Phase III & Phase IV Verna Industrial Estate, Verna, Salcette Goa-403722 India
Active Pharmaceutical Ingredient (API):	Lamivudine/Nevirapine/Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, combinations, J05AR05
Therapeutic indication:	[HA629 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg.

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

1. Introduction

[HA629 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25kg.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA629 trade name], should be initiated by 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 (APIs)

Lamivudine

Based on scientific principles, WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble. Lamivudine API is described in the Ph. Int, Ph. Eur and USP, and is considered well-established in the WHO PQTm.

The API specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR and HPLC), light absorption, water content (KF), limit of lamivudine enantiomer ($\leq 0.30\%$), residual solvents (GC), chromatographic purity (HPLC), assay (HPLC), residue on ignition, particle size, bulk density, methane sulfonates (GC-MS; each ≤ 5 ppm) and toluene sulfonates (GC-MS; each ≤ 5 ppm).

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.

Nevirapine

Nevirapine exists in two crystal forms: the anhydrous form and the hemihydrate. Anhydrous nevirapine is used in the manufacture of the tablets. Anhydrous nevirapine is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQTm.

Anhydrous nevirapine is adequately controlled by its pharmacopoeial based specifications which include tests for description, solubility, identification (IR, HPLC), water content (KF), residue on ignition, specified and unspecified impurities (HPLC), assay (HPLC), residual solvents (GC), bulk density, particle size and identification of polymorph.

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.

Zidovudine

Based on scientific principles, WHO PQTm has identified zidovudine (up to 300 mg oral dose) as a BCS class 1 API. The API is thus BCS highly soluble. Zidovudine API is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQTm.

The zidovudine specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), melting point, specific optical rotation, water content (KF), residue on ignition, chromatographic purity (TLC and HPLC), assay (HPLC), residual solvents (GC), particle size,

bulk density, methyl p-toluene sulfonate (LC-MS; ≤ 2.5 ppm) and methyl methane sulfonate (LC-MS; ≤ 2.5 ppm).

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.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG and polysorbate. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white coloured, capsule-shaped, bevelled edged, biconvex, film-coated tablet, debossed with 'I' on one side and '47' on the other side. The tablets are packaged in Alu-PVC/PVDC blister and in a white, opaque HDPE bottle closed with a white polypropylene child-resistant cap.

The aim of formulation development was to develop Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg tablets with similar quality profile as the WHO-recommended comparator products Combivir® (lamivudine and zidovudine) Tablets 150mg/300mg and Viramune® (nevirapine) Tablets 200mg. The excipients used in the formulation are well-established, with similar function as that of the excipients in the WHO-recommended comparator products. No evidence of chemical or physical incompatibility was detected during controlled API-API and API-excipient studies. Wet granulation was selected as the appropriate manufacturing method to improve the flow properties of the API and blend. Several trials were conducted to optimize the formulation as well as the manufacturing process. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (HPLC and TLC), average weight, uniformity of weight, tablet dimensions, disintegration time, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 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 packages proposed for marketing of the product. With the exception of water content which showed a slight increasing trend but within limits, the product proved to be quite stable 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 Bio-Equivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

An open label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose oral bioavailability study of Lamivudine, Zidovudine and Nevirapine tablets 150 /300 /200 mg (Test) of Micro Labs Ltd, India and Combivir® (lamivudine and zidovudine) tablets 150 mg/ 300 mg (Reference 1) of ViiV Healthcare, Research Triangle Park, NC 27709 and Viramune® (nevirapine) tablets 200 mg (Reference 2) of Boehringer Ingelheim Pharmaceuticals, Inc., USA (R=R1+R2) in healthy, adult, human subjects under fasting conditions. (Study no. 465-16).

The objective of the study was to compare the bioavailability of the stated Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300 mg FDC tablet manufactured by/for Micro Labs Ltd., India (test drug) with the reference formulations Combivir® (ViiV Healthcare Ltd.) and Viramune® (Boehringer Ingelheim Pharmaceuticals, 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 [HA629 trade name] (lamivudine 150 mg + nevirapine 200 mg + zidovudine 300 mg)
Batch no. LNAG002.
Treatment R: Reference – 1 tablet Combivir® (lamivudine 150 mg + zidovudine 300 mg)
Batch no. 6ZP4618.
– 1 tablet Viramune® (nevirapine 200 mg)
Batch no. 462288F

A 27-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 29 samples within 72 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, nevirapine and zidovudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for lamivudine, 15 ng/mL for nevirapine and 10 ng/mL for zidovudine.

The study was performed with 78 participants; data generated from a total of 76 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)[#]	1.50 (0.5 – 5.5)	1.50 (0.33 – 4.67)	-	-
C_{max} (ng/mL)	1375 ± 427 (1314)	1340 ± 391 (1285)	102.2	96.4 – 108.5

AUC_{0-t} (ng·h/mL)	6565 ± 1656 (6361)	6551 ± 1670 (6347)	100.2	97.0 – 103.5
AUC_{0-inf} (ng·h/mL)	6742 ± 1648 (6546)	6736 ± 1670 (6538)	100.1	97.0 – 103.3

* geometric mean; #median (range)

Nevirapine

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) #	2.5 (0.5 – 24.0)	3.0 (0.5 – 24.0)	-	-
C_{max} (ng/mL)	2470 ± 619 (2397)	2534 ± 605 (2468)	97.2	93.3 – 101.2
AUC_{0-72h} (ng·h/mL)	107712 ± 20913 (105798)	109807 ± 19964 (108080)	97.9	96.4 – 99.4

* geometric mean; #median (range)

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) #	0.75 (0.25 – 3.5)	0.5 (0.17 – 3.25)	-	-
C_{max} (ng/mL)	2161 ± 1329 (1818)	2179 ± 1140 (1911)	95.2	83.3 – 108.8
AUC_{0-t} (ng·h/mL)	2881 ± 845 (2761)	2894 ± 826 (2785)	99.1	95.5 – 102.9
AUC_{0-inf} (ng·h/mL)	2909 ± 850 (2787)	2922 ± 834 (2812)	99.1	95.5 – 102.9

* geometric mean; #median (range)

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine, nevirapine and zidovudine. Accordingly, the test

Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Combivir® (ViiV Healtcare UK Ltd.) and Viramune® (Boehringer Ingelheim Pharmaceuticals, Inc.).

4. Summary of Product Safety and Efficacy

[HA629 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 product.

According to the submitted data on quality and bioavailability, [HA629 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO-recommended comparator products Combivir® and Viramune® 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 [HA629 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA629 trade name] has shown to be bioequivalent with Combivir® [(lamivudine/zidovudine 150mg/300mg tablets), GlaxoSmithKline] and Viramune® [(nevirapine 200 mg tablets), Boehringer Ingelheim Pharmaceuticals Inc.].

Efficacy and Safety

Regarding clinical efficacy and safety, [HA629 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 [HA629 trade name] was acceptable for the following indication: **"the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg"** and has advised that the quality, efficacy and safety of [HA629 trade name] allow inclusion of [HA629 trade name] , manufactured at Micro Labs Limited Plot No: S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Salcette, Goa-403722,India ,in the list of prequalified medicinal products.