SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Lamivudine/Zidovudine 150 mg/300 mg Tablets[1]
Manufacturer of Prequalified Product:	Strides Arcolab Limited 36/7, Suragajakknahalli Indlavadi Cross, Anekal Taluk Bangalore-562 106 India
Active Pharmaceutical Ingredients (APIs):	Lamivudine & Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR10)
Therapeutic indication:	Lamivudine/Zidovudine 150 mg/300 mg Tablets is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing 25 kg or more.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Lamivudine/Zidovudine 150 mg/300 mg Tablets is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing over 25kg.

Lamivudine/Zidovudine 150 mg/300 mg Tablets should be prescribed by a health care provider experienced in the management of HIV infection.

2. Assessment of Quality

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

Active pharmaceutical Ingredients (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 API and zidovudine API are both described in the Ph.Int., Ph.Eur. and the USP 29.
The APIs, which are obtained from approved API manufacturers, are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications for residual solvents.
Based on the results of stability testing conducted according to the requirements of WHO, a two-year retest period was approved for both APIs.

Other ingredients
Other ingredients used in the tablet core formulation include colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, povidone, purified talc and sodium starch glycollate.
The film coat contains hypromellose, polyethylene glycol 400 and titanium dioxide. A declaration was provided that magnesium stearate is BSE/TSE free.

Finished pharmaceutical product (FPP)
Lamivudine 150 mg & Zidovudine 300 mg tablets is white to off white, oval shaped, film-coated tablets with "LZ" debossed on one side and plain on the other side. The tablets are packaged in an HDPE container with LDPE cap.
The development of the final composition has been described. The selection of excipients was based on feasibility studies. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.
The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.
Stability studies have been performed at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. The results are well within the agreed specifications, and support the conclusion that the formulation is stable for the duration of the testing period.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

A randomized, open-label, two period, single dose, crossover bioequivalence study on Lamivudine/Zidovudine 150/300 mg tablets (Strides Arcolab Ltd., India) comparing with Combivir tablets (Lamivudine/Zidovudine 150/300 mg; manufactured by GlaxoSmithKline, USA) in 32 healthy, adult male and female volunteers under fasting conditions (study number 581/05).

The objective of the study was to compare the bioavailability of the stated test formulation manufactured by Strides Arcolab Ltd., India (test drug) with the same dose of the reference and to

assess bioequivalence. The comparison was performed as a single centre, crossover study in healthy subjects. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – Lamivudine/Zidovudine 150/300 mg tablets (Lamivudine/Zidovudine 150/300 mg) Batch No. 7200283
Treatment R: Reference – Combivir tablets (Lamivudine/Zidovudine 150/300 mg), Batch No. 4ZP1764

A 6 day wash-out period was observed between administration of test and reference. Serial blood samples (1 predose sample and 20 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for Lamivudine/Zidovudine in plasma were analyzed using a validated LC-MS/MS method. Limit of quantification was stated to be 0.0219 µg/ml for Lamivudine and 0.0224 µg/ml for Zidovudine.

The study was performed with 32 volunteers; however one subject was withdrawn due to adverse events. Accordingly, data generated from 31 participating subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Geometric means (AUC, Cmax) and arithmetic means (tmax) and statistical results for lamivudine (150 mg; n=31) are summarised in the following table:

Lamivudine

Pharmacokinetic Parameter	Test formulation (T) arithm.mean (CV*)	Reference (R) arithm.mean (CV*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.71(0.41**)	0.98 (0.38**)	-	-
C_{max} (µg/ml)	1.7219 (2.328)	1.744 (30.18)	100.08	90.63 – 110.52
AUC_{0-t} (µg.h/ml)	6.7787 (20.41)	6.6894 (23.69)	102.13	96.31 – 108.29
AUC_{0-inf} (µg.h/ml)	7.0128 (19.8)	6.9239 (22.88)	102.01	96.42 – 107.92

*) interindividual coefficient of variation
**) SD

Geometric means (AUC, C_{max}) and arithmetic means (t_{max}) and statistical results for zidovudine (300 mg; n=31) are summarised in the following table:

Zidovudine

Pharmacokinetic Parameter	Test formulation (T) arithm.mean (CV*)	Reference (R) arithm.mean (CV*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.48 (0.21**)	0.49 (0.23**)	-	-
C_{max} (µg/ml)	2.8388 (38.64)	2.8924 (30.52)	95.55	81.15 – 112.51
AUC_{0-t} (µg.h/ml)	2.7795 (21.71)	2.8004 (21.28)	98.89	92.77 – 105.41
AUC_{0-inf} (µg.h/ml)	2.8443 (21.43)	2.8689 (20.53)	98.70	92.63 – 105.15

*) interindividual coefficient of variation
**) SD

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by AUC and C_{max} values. Accordingly, the test product Lamivudine/Zidovudine 150/300 mg tablets meets the criteria for bioequivalence with regard to extent and rate of absorption and is bioequivalent to the reference Combivir tablets.

4. Summary of Product Safety and Efficacy

Lamivudine/Zidovudine 150 mg/300 mg Tablets has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator`s product. According to the submitted data on quality and bioavailability Lamivudine/Zidovudine 150 mg/300 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Combivir 150 mg/300 mg tablets 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 consideration. 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 clincial performance when Lamivudine/Zidovudine 150 mg/300 mg Tablets is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

Lamivudine/Zidovudine 150 mg/300 mg Tablets has shown to be bioequivalent Combivir tablets (lamivudine 150 mg + zidovudine 300 mg combination tablet, GlaxoSmithKline, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine/Zidovudine 150 mg/300 mg Tablets is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO´s assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of Lamivudine/Zidovudine 150 mg/300 mg Tablets was acceptable for the following indication: **in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over 12 years of age** and has advised that the quality, efficacy and safety of Lamivudine/Zidovudine 150 mg/300 mg Tablets allow inclusion of Lamivudine/Zidovudine 150 mg/300 mg Tablets, manufactured at Strides Arcolab Limited 36/7, Suragajakknahalli Indlavadi Cross, Anekal Taluk Bangalore-562 106 India in the list of prequalified medicinal products.