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.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Lamivudine and Zidovudine Tablets 150 + 300 mg*
Manufacturer of Prequalified Product:	Ranbaxy Laboratories Limited Paonta Sahib, District Sirmour Himachal Pradesh 173025 India.
International Nonproprietary Name:	Lamivudine and zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR01)
Therapeutic indication:	Lamivudine and Zidovudine Tablets 150 + 300 mg is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over 12 years of age

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Lamivudine and Zidovudine Tablets 150 + 300 mg is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over 12 years of age

2. Assessment of Quality

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

Active Pharmaceutical Ingredients (APIs)

Lamivudine and zidovudine
Lamivudine and zidovudine are APIs used in several prequalified FPPs containing the individual APIs alone or in FDCs with other APIs. The quality of the two APIs is therefore well established.

Lamivudine
(-)-4-amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one is controlled according to the requirements of major internationally used pharmacopoeiae. Lamivudine is manufactured by a multistep synthesis. Quality specifications of the starting materials and intermediate stages of synthesis were adequately controlled to result in a consistent quality of the lamivudine.
The results of forced degradation studies revealed that Lamivudine was stable upon exposure to white fluorescent light, heat and UV light.
Lamivudine exists in two polymorphic forms. Form II polymorph is used in Lamivudine and Zidovudine Tablets 150 + 300 mg .
A retest period of 24 months was prequalified for Lamivudine when stored in the proposed well-closed, light resistant containers at a temperature not exceeding 30^{o}C.

Zidovudine
1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione is controlled according to the requirements of major internationally used pharmacopoeiae. Quality specifications of the starting materials and intermediate stages of synthesis were adequately controlled to result in a consistent quality of the zidovudine.
In stress stability studies, zidovudine was sensitive to UV light.
A retest period of 24 months was prequalified for Zidovudine, when stored in the proposed tight, light resistant containers at a temperature not exceeding 30^{o}C.

Other ingredients

All the excipients in the tablet core are described in the monograpbs of internationally used major pharmacopoeiae. The film-coat is an Opadry, whose components — Propylene Glycol, Hypromellose and Titanium Dioxide (colouring agent)— are described in the Ph. Eur. and the USP.
A certificate was provided from the stated manufacturer the magnesium stearate is TSE free. An assurance was provided that all other ingredients in the FPP are not of animal origin.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development
Pharmaceutical development is described in the expert report, which extensively covers details of Lamivudine chemistry, Zidovudine chemistry, drug product description, compatibility studies, prototype formulation development, selection of suitable manufacturing process, optimization of the formulation, in process holding time, moisture uptake study, final composition, manufacturing process and its validation, control of excipients, control of drug product, container closure system, bioequivalence study results and stability data on the product.

Evaluation of batch analytical results of the three validation batches revealed that the manufacturing process had reliably produced the FPP that met predetermined specifications.
The specifications and associated control methods are relevant to a tablet formulation and are acceptable. Tests at release are standard and include among others limits for assay, degradation products, and dissolution. These tests should ensure reproducible clinical performance of the product.

Stability testing
Three primary stability batches were studied in HDPE bottles, under prequalification conditions: 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5%RH. Both the accelerated and the long-term stability data showed little degradation and little variability.
A shelf life of 24 months was prequalified for Lamivudine and Zidovudine Tablets 150 + 300 mg, when stored in the proposed packing material, protected from light and at a temperature not exceeding 30^{o}C.

Conclusions

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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, bioavailability study comparing a fixed-dose combination of lamivudine 150 mg and zidovudine 300 mg tablets (Lamivudine and Zidovudine Tablets 150 + 300 mg, Ranbaxy Laboratories Ltd., India), with Combivir® tablets (fixed-dose combination of lamivudine 150 mg and zidovudine 300 mg) by GlaxoSmithKline, UK in healthy adult human subjects under fasting conditions (Study No. B055507).

The objective of the study was to compare the bioavailability of the stated fixed-dose combination product manufactured by Ranbaxy Laboratories Ltd., India (test drug) with the same dose of the reference product and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male and female 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 150mg / zidovudine 300 mg) Batch No. 1440444
Treatment R:	Reference – Combivir® 150/300 mg tablets (lamivudine 150mg / zidovudine 300 mg) Batch No. 4ZP1764

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 predose sample and 24 samples within 36 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 lamivudine and zidovudine in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 6.0 ng/ml for both, lamivudine and zidovudine.

The study was performed with 68+2 participants, data generated from a total of 62 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Geometric means (AUC, C_{max}) and arithmetic means (t_{max}) for lamivudine and zidovudine as well as statistical results are summarised in the following tables:

Lamivudine

Pharmacokinetic Parameter	Test (T) geom. means (CV%)	Reference (R) geom. means (CV%)	log-transformed parameters	
			Ratio of least square means T/R (%)	ANOVA 90% CI (%)
AUC_{0-t} (ng.h/ml)	5570.9 (26.0)	5511.7 (26.6)	101	97.8-105
$AUC_{0-\infty}$ (ng.h/ml)	5729.3 (25.3)	5658.7 (26.1)	102	98.2-105
C_{max} (ng/ml)	1554.6 (34.1)	1517.1 (32.9)	103	96.8-109
t_{max} (h) *	1.226 (59.1)	1.177 (54.2)	-	-

* arithmetic mean (CV%)

Zidovudine

Pharmacokinetic Parameter	Test (T) geom. means (CV%)	Reference (R) geom. means (CV%)	log-transformed parameters	
			Ratio of least square means T/R (%)	ANOVA 90% CI (%)
AUC_{0-t} (ng.h/ml)	2006.6 (46.0)	2007.0 (32.4)	97.9	93.7-102
$AUC_{0-\infty}$ (ng.h/ml)	2034.9 (46.9)	2031.7 (32.1)	97.9	93.7-102
C_{max} (ng/ml)	1623.0 (46.6)	1697.6 (46.5)	96.1	85.5-108
t_{max} (h) *	0.868 (99.1)	0.777 (84.9)	-	-

* arithmetic mean (CV%)

Conclusions:

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

4. Summary of Product Safety and Efficacy

Lamivudine and Zidovudine Tablets 150 + 300 mg have 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 it 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 presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

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

Efficacy and Safety

Regarding clinical efficacy and safety, lamivudine/zidovudine are 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 assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of Lamivudine and Zidovudine Tablets 150 + 300 mg 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 to include Lamivudine and Zidovudine Tablets 150 + 300 mg, manufactured at Ranbaxy Laboratories Limited, Paonta Sahib, District Sirmour Himachal Pradesh 173025, India in the list of prequalified medicinal products.