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:	[HA524 trade name] *
Manufacturer of Prequalified Product:	Strides Arcolab Limited 36/7, Suragajakkanahalli Indlavadi cross Anekal Taluk Bangalore – 562 106 India.
Active Pharmaceutical Ingredients (APIs):	lamivudine, nevirapine, zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR05)
Therapeutic indication:	Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg 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

Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg.

Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg should be prescribed by a physician experienced in the management of HIV infection.

2 Assessment of Quality

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

Active pharmaceutical Ingredients (APIs)

Lamivudine

Based on scientific principles the WHO PQT-M has identified lamivudine (up to 300mg 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 the USP, and considered well-established in the WHO PQT-M.

The lamivudine specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), light absorption, water content, limit of lamivudine enantiomer (chiral HPLC, $\leq$ 0.3%), chromatographic purity (HPLC), assay (HPLC), residual solvents, melting range, residue on ignition, heavy metals, particle size distribution and foreign matter.

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 is a weak base class 2 API 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*).

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 PQT-M.

Anhydrous nevirapine is adequately controlled by its pharmacopoeial based specifications which include tests for description, solubility, identification (IR and HPLC), water content, residue on ignition, heavy metals, organic impurities (HPLC), assay (HPLC), residual solvents, melting range, foreign matter, particle size and polymorphic form (XRPD).

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 the WHO PQT-M has identified zidovudine (up to 300 mg oral dose) as a BCS class 1 API. The APIs 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 PQT-M.

The zidovudine specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), specific optical rotation, water content, loss on drying, residue on ignition, heavy metals, chromatographic purity (TLC and HPLC), assay (HPLC), residual solvents, particle size distribution, foreign matter, bulk and tapped density, melting range and appearance of solution. Methylmethane sulfonate and ethyl-4-toluene sulfonate content is also controlled on material received from one of the suppliers.

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 microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, talc and magnesium stearate. Magnesium stearate is obtained from vegetable origin. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, and polyethylene glycol 400.

Finished pharmaceutical products (FPP)

Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg are white coloured, capsule shaped, film-coated tablets engraved "ZLN" on one side and plain on the other side. The tablets are packaged in HDPE bottles with child resistant caps or screw caps with induction seal liner.

Pharmaceutical development and manufacture

The development of the final composition of product has been described. The objective was to develop a stable product, bioequivalent to the comparator products Combivir® (containing 150 mg lamivudine and 300 mg zidovudine) and Viramune® (containing 200 mg of nevirapine). The selection of excipients was based on their suitability to achieve the desired tablet characteristics and compatibility with the APIs. The core tablets were manufactured via a standard wet granulation process. Optimum levels of the functional excipients in the formulation ensured dissolution profiles similar to those of the comparator products and acceptable physical characteristics of the tablets. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include appropriate tests for description, identification of the APIs (HPLC and TLC), average weight, uniformity of weight, tablet dimensions, disintegration time, dissolution (HPLC detection), water content, related substances (HPLC), uniformity of dosage units (by content uniformity), assay (HPLC) and microbial limits.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed little change with time and were well within the justified specifications at all 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 Bioequivalence

The following bioequivalence study has been performed in 2008 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of fixed dose combination tablets containing Lamivudine, Nevirapine and Zidovudine (150/200/300mg) of Strides Arcolab Limited, India and Combivir® (Lamivudine/Zidovudine) Tablets 150mg/300mg of GlaxoSmithKline, Research Triangle Park, NC 27709 and Viramune® (Nevirapine) Tablets 200mg of Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT 06877 USA in healthy, adult, human subjects under fasting conditions. (study no. 08-VIN-047).

The objective of the study was to compare the bioavailability of the stated Lamivudine/ Nevirapine/Zidovudine 150/200/300 mg FDC tablet manufactured by Strides Arcolab Ltd., India (test drug) with the same dose of the individual reference formulations (Combivir®, GSK and Viramune® Boehringer Ingelheim Pharmaceuticals) 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 Lamivudine/ Nevirapine/Zidovudine 150/200/300 mg (lamivudine 150 mg + nevirapine 200 mg + zidovudine 300 mg) Batch no. 7205127.

Treatment R: Reference –
1 tablet Combivir®
(lamivudine 150 mg + zidovudine 300 mg)
Batch no. 7ZP0605.
1 tablet Viramune®
(nevirapine 200 mg)
Batch no. 757739A.

A 23 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 30 samples within 72 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, zidovudine and nevirapine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for lamivudine, zidovudine as well as for nevirapine.

The study was performed with 64 participants; data generated from a total of 61 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine, zidovudine and nevirapine 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)	1.19 ± 0.69	1.42 ± 0.71	-	-
C_{max} (ng/ml)	1582 ± 492 (1502)	1472 ± 466 (1401)	107.3	100.4 – 114.6
AUC_{0-t} (ng.h/ml)	5950 ± 1282 (5817)	5990 ± 1486 (5788)	100.5	96.0 – 105.2
AUC_{0-inf} (ng.h/ml)	6312 ± 1341 (6175)	6391 ± 1589 (6178)	99.9	95.6 – 104.5

* 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)	0.56 ± 0.49	0.78 ± 0.64	-	-
C_{max} (ng/ml)	2735 ± 1151 (2474)	2317 ± 1037 (2085)	118.6	105.5 – 133.4
AUC_{0-t} (ng.h/ml)	2796 ± 617 (2732)	2771 ± 636 (2703)	101.1	96.9 – 105.4
AUC_{0-inf} (ng.h/ml)	2896 ± 624 (2833)	2871 ± 640 (2805)	101.0	97.0 – 105.1

* geometric mean

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)	3.90 ± 4.04	2.76 ± 2.04	-	-
C_{max} (ng/ml)	2127 ± 349 (2097)	2356 ± 411 (2322)	90.3	87.0 – 93.8
AUC_{0-72h} (ng.h/ml)	95727 ± 16114 (94413)	97489 ± 17037 (96092)	98.3	96.5 – 100.0

* geometric mean

Conclusion

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 nevirapine. For zidovudine the criteria were met for AUC. Additional data were submitted to support a biowaiver for zidovudine. Additional data were submitted to support a biowaiver for zidovudine, a BCS Class I API. Dissolution data at a pH 1.2, 4.5 and 6.8 showed that Test and Reference were comparable, i.e. more than 85% dissolved within 15 min. Furthermore, a Tentative Approval letter by the FDA was submitted for the Test, which means that it has been approved by a stringent ICH Regulatory Authority. As such, the product is considered acceptable.

4. Summary of Product Safety and Efficacy

Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products Combivir® and Viramune® 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 Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg is used in accordance with the SmPC.

Bioequivalence

Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg has shown to be bioequivalent with Combivir® tablets (150 mg lamivudine + 300 mg zidovudine), GlaxoSmithKline, USA, and Viramune® tablets (200 mg nevirapine), Boehringer Ingelheim Pharmaceuticals Inc., USA.

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg was acceptable for the following indication: **"treatment of HIV-1 infected adults, and children weighing at least 25 kg"** and has advised that the quality, efficacy and safety of Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg allow inclusion of Lamivudine/Nevirapine/Zidovudine Tablets, Film Coated, 150mg/200mg/300mg, manufactured at Strides Arcolab Limited, 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk, Bangalore – 562 106, India in the list of prequalified medicinal products.