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:	[HA557 trade name] *
Manufacturer of Prequalified Product:	Strides Shasun Limited 36/7, Suragajakkanahalli Indlavadi cross Anekal Taluk Bangalore – 562 106 India. Tel : 91-80-67840600 Email : sadiq.basha@strides.com
Active Pharmaceutical Ingredients (APIs):	Lamivudine/Nevirapine/Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, combinations, J05AR05
Therapeutic indication:	[HA557 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected children weighing less than 25 kg.

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

‡ Formerly Strides Shasun Ltd

1. Introduction

Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible tablets is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected children weighing less than 25 kg. Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible tablets should be prescribed 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 Ingredients (APIs)

Lamivudine

Based on scientific principles the WHO Prequalification Team – Medicines (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 PQP.

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

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 dispersible tablets. Anhydrous nevirapine is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQP.

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

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 PQP.

The zidovudine specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), specific optical rotation, water content(KF) / 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 point/range and appearance of solution. Methylmethane sulfonate and methyl-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 dispersible tablet formulation include lactose monohydrate (from vegetable origin), microcrystalline cellulose, sodium starch glycolate, sucralose, povidone, colloidal silicon dioxide, magnesium stearate and flavour strawberry. Attestations have been submitted confirming BSE/TSE-free status of all the ingredients.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture

The dispersible tablets are white to off-white circular biconvex tablets, engraved “LNZ” on one side and break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies during development. The tablets are packaged in a HDPE bottles with child resistant caps or screw caps with induction seal liner.

The objective of the development studies was to obtain a fixed-dose combination dispersible tablet of lamivudine/nevirapine/zidovudine 30mg/50mg/60mg which is stable and bioequivalent to the following comparator products, taken concomitantly in suitable quantities: Epivir® oral solution (containing 10mg/ml of lamivudine), Viramune® tablets (containing 200 mg of nevirapine anhydrous) and Retrovir® syrup (containing 50mg/5ml of zidovudine). The selection and optimisation of excipients were based on their suitability to achieve the desired tablet characteristics and compatibility with the APIs. The tablets are manufactured via a standard wet granulation process. All critical steps of the manufacturing process were optimized as discussed in the product development report. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Product specifications

The finished product specifications include appropriate tests for description, identification of the APIs (HPLC and TLC), average weight, uniformity of weight, uniformity of dosage units (by content uniformity), disintegration time (≤ 3 minutes), fineness of dispersion, water content (KF), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents 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 2010 according to internationally accepted guidelines.

An open label, randomized, balanced, two treatment, two period, two sequence, two way crossover, single dose comparative oral bioavailability study of Lamivudine, Nevirapine and Zidovudine for oral suspension [30/50/60 mg] of Strides Shasun Limited, India with Epivir® oral solution (lamivudine oral solution) 10mg/mL of GlaxoSmithKline, Research Triangle Park, NC 27709, Retrovir® (zidovudine) syrup 50mg/5mL 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 condition. (study no. 10-VIN-129).

The objective of the study was to compare the bioavailability of the stated Lamivudine/ Nevirapine/Zidovudine 30/50/60 mg FDC tablet for oral suspension by Strides Shasun Ltd., India (test drug) with the same dose of the individual reference formulations (Epivir® oral solution, GSK, Retrovir® syrup, 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 – 4 tablets Lamivudine/Nevirapine/Zidovudine 30/50/60 mg (lamivudine 120 mg + nevirapine 200 mg + zidovudine 240 mg) Batch no. 7209229.
Treatment R:	Reference – 12 ml Epivir® 10mg/ml oral solution (lamivudine 120 mg) Batch no. 0A001. 1 tablet Viramune® (nevirapine 200 mg) Batch no. 958899A. 24 ml Retrovir® 50mg/5ml syrup (zidovudine 240 mg) Batch no. 8M002.

The Lamivudine/Nevirapine/Zidovudine 30/50/60 mg Test tablet was dispersed in water before intake. 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 40 ng/ml for lamivudine, 60 ng/ml for zidovudine and 50 ng/ml for nevirapine.

The study was performed with 57 participants; data generated from a total of 42 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)	0.92 ± 0.56	1.06 ± 0.67	-	-
C_{max} (ng/ml)	1404 ± 456 (1331)	1227 ± 344 (1180)	112.8	106.2 – 119.8
AUC_{0-t} (ng.h/ml)	5221 ± 1177 (5083)	4910 ± 1023 (4805)	105.8	101.4 – 110.4
AUC_{0-inf} (ng.h/ml)	5541 ± 1220 (5399)	5236 ± 1067 (5129)	105.3	101.1 – 109.7

* 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)	0.34 ± 0.19	0.44 ± 0.19	-	-
C_{max} (ng/ml)	2603 ± 1014 (2388)	2173 ± 691 (2057)	116.1	105.6 – 127.6
AUC_{0-t} (ng.h/ml)	2359 ± 700 (2261)	2140 ± 554 (2075)	108.9	105.2 – 112.8
AUC_{0-inf} (ng.h/ml)	2491 ± 731 (2392)	2264 ± 566 (2200)	108.7	105.0 – 112.5

* 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)	1.85 ± 1.05	5.45 ± 5.30	-	-
C_{max} (ng/ml)	2684 ± 393 (2656)	2452 ± 488 (2403)	110.5	106.5 – 114.7
AUC_{0-72h} (ng.h/ml)	107690 ± 14271 (106802)	107489 ± 13428 (106656)	100.1	98.5 – 101.8

* geometric mean

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 nevirapine. For zidovudine the criteria were met for AUC. Additional data were submitted to support a biowaiver for zidovudine. 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 minutes. In addition, it has been proven that the administered zidovudine dose was completely soluble in 40 ml of water. 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 30/50/60mg dispersible tablets 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 30/50/60mg Dispersible Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual references Epivir oral solution (GlaxoSmithKline), Viramune oral suspension (Boehringer Ingelheim) and Retrovir syrup (GlaxoSmithKline) 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 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 30/50/60mg dispersible tablets is used in accordance with the SmPC.

Bioequivalence

Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible tablets has shown to be bioequivalent with the separate reference formulations Epivir oral solution (GlaxoSmithKline), Viramune oral suspension (Boehringer Ingelheim) and Retrovir syrup (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible 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/Nevirapine/Zidovudine 30/50/60mg dispersible tablets was acceptable for the following indication: **"for treatment of Human Immunodeficiency Virus (HIV) infection in children weighing less than 25 kg"** and has advised that the quality, efficacy and safety of Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible tablets allow inclusion of Lamivudine/Nevirapine/Zidovudine 30/50/60mg dispersible tablet, manufactured at Strides Shasun Limited, 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk, Bangalore - 562106, India in the list of prequalified medicinal products