This part outlines 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	[HA572 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No. H-12 & H-13 MIDC, Waluj Industrial Area Aurangabad – 431136 Maharashtra State India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine and zidovudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections,combinations (J05AR01)
Therapeutic indication	[HA572 trade name]is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

1. Introduction

[HA572 trade name] is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

[HA572 trade name] should be prescribed by a physician 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 (API)

Based on scientific principles the WHO Prequalification of Medicines Programme has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API and zidovudine (up to 300 mg oral dose) as a BCS class 1 API. Lamivudine and zidovudine are thus highly soluble in aqueous medium over the pH range 1.0 – 6.8.

Lamivudine and zidovudine have been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that these two APIs, used in the manufacture of [HA572 trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components:

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

Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, croscarmellose sodium, aspartame, magnesium stearate and strawberry flavour (containing natural flavours and maltodextrin). TSE/BSE free certificates were provided for these excipients. All excipients, except strawberry flavour which is controlled with in-house specifications, are declared to be of compendial grade.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA572 trade name]is a white to off-white, round, biconvex tablet debossed with "M" on one side of the tablet and a score-line on the other side, with "LZ" debossed to the left and "1" to the right of the score-line. The score-line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in a round wide mouth opaque white HDPE bottle with white opaque polypropylene screw cap, and containing absorbent cotton.

The development of the final composition of [HA572 trade name] has been described. The objective was to develop a fixed-dose combination dispersible tablet containing of 30 mg lamivudine and 60 mg zidovudine which is stable and bioequivalent to the following innovator products, taken concomitantly in suitable quantities: Epivir® oral solution (containing 10mg/ml of lamivudine) and Retrovir® syrup (containing 50mg/5ml of zidovudine).

Examination of the physical properties of the lamivudine and zidovudine indicated that the APIs exhibit acceptable flow characteristics for manufacture of the tablets via direct compression. The excipients selected are conventional pharmaceutical ingredients, suitable for the intended purpose and compatible with the APIs. Various studies were performed to optimize the concentration of the excipients and process parameters in order to obtain the finished product of desired characteristics Strawberry flavour and aspartame were selected as flavouring agent and sweetener, respectively, and their concentrations were optimized to obtain the desired effects. The tablets showed rapid disintegration and very rapid dissolution properties. Appropriate in-process controls were set to ensure batch-to-batch reproducibility

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), loss on drying, friability, disintegration time (≤ 3 minutes), fineness of dispersion, microbial enumeration and specified microorganisms and uniformity of mass for subdivided tablets. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been performed at 30□C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at both storage conditions; the stability parameters showed no negative trend. 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 2012 according to internationally accepted guidelines:

An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of test product [HA572 trade name](2 x lamivudine / zidovudine 30 mg / 60 mg dispersible tablets) of Mylan Laboratories Limited, India and Reference products 'EPIVIR' (lamivudine) oral solution 10 mg/ml (1 x 6 ml) and 'RETROVIR®' (zidovudine) syrup 50 mg/5 ml (1 x 12 ml) of Viiv Healthcare, Research Triangle Park, NC 27709 in healthy adult human subjects under fasting conditions (study no. BA12101402-01).

The objective of the study was to compare the bioavailability of the stated [HA572 trade name] manufactured by Mylan Laboratories Limited, India (test drug) with the same dose of the individual reference formulations (Epivir®, oral solution, Viiv Healthcare, and Retrovir®, oral solution, Viiv Healthcare) 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 – 2 tablets [HA572 trade name] (dissolved prior administration)
(lamivudine 60 mg + zidovudine 120 mg) Batch no. 1108645.

Treatment R: References
- 6 ml Epivir® 10 mg/ml oral solution (lamivudine 60mg) Batch no. 1L005.
- 12 ml Retrovir® 10 mg/ml oral solution (zidovudine 120 mg) Batch no. 0L002.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 21 samples within 24 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 were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/ml for lamivudine and 10 ng/ml for zidovudine.

The study was performed with 48 participants; data generated from a total of 46 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Lamivudine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.83 (0.50 – 2.50)	0.83 (0.50 – 3.0)	–	–
C_{max} (ng/mL)	667 ± 199 (637)	666 ± 206 (635)	100.3	94.4 – 106.7
AUC_{0-t} (ng·h/mL)	2989 ± 687 (2900)	2970 ± 604 (2905)	99.9	96.3 – 103.6
AUC_{0-inf} (ng·h/mL)	3105 ± 691 (3019)	3090 ± 614 (3026)	99.8	96.4 – 103.3

Zidovudine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.33 (0.17 – 0.83)	0.33 (0.17 – 0.83)	–	–
C_{max} (ng/mL)	866 ± 288 (821)	943 ± 350 (882)	93.1	85.7 – 101.2
AUC_{0-t} (ng·h/mL)	1101 ± 268 (1069)	1113 ± 305 (1073)	99.7	96.5 – 102.9
AUC_{0-inf} (ng·h/mL)	1131 ± 269 (1100)	1144 ± 308 (1104)	99.7	96.6 – 102.8

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 dispersible tablet [HA572 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual references Epivir® 10 mg/ml oral solution (Viiv Healthcare) and Retrovir® 50 mg/5ml oral solution (Viiv Healthcare).

4. Summary of product safety and efficacy

[HA572 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [HA572 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual innovator products Epivir (lamivudine) 10 mg/ml solution and Retrovir (zidovudine) 10 mg/ml solution (Viiv Healthcare) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA572 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer 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 [HA572 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA572 trade name] has been shown to be bioequivalent with Epivir® 10 mg/ml oral solution (Viiv Healthcare) and Retrovir® 50 mg/5ml oral solution (Viiv Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA572 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC 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 [HA572 trade name] was acceptable for the following indication: 'in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infection in children', and would allow inclusion of [HA572 trade name], manufactured at Mylan Laboratories Limited, Waluj Industrial Area, Aurangabad - 431136, Maharashtra State, India in the list of prequalified medicinal products.