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:	[HA433 trade name][*]
Manufacturer of Prequalified Product:	Matrix Laboratories Limited 1-1-151/1, 5th Floor Sairam Towers Alexander Road 500 003 Secunderabad India Phone: +91 40 2348 0042
Active Pharmaceutical Ingredients (APIs):	Lamivudine/Nevirapine/Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, combinations, J05AR05
Therapeutic indication:	[HA433 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.
[1] Formerly Matrix Laboratories Ltd

1. Introduction

[HA433 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected children weighing less than 25 kg. [HA433 trade name] is not indicated for use in patients with clinically significant hypersensitivity to lamivudine, zidovudine and/or nevirapine or to any of the components contained in the formulation. It is recommended that therapy is given only 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 and zidovudine are class 1 APIs and nevirapine 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 FPP.

Lamivudine API, anhydrous nevirapine API and zidovudine API are all described in the Ph.Int., Ph.Eur. and the USP, and are considered well-established in the Prequalification Programme.

The APIs, which are obtained from approved manufacturers, are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications including residual solvents and particle size distribution.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months was approved for lamivudine, nevirapine and zidovudine.

Other ingredients

Other ingredients used in the tablet formulation include acesulfame potassium, aspartame, colloidal silicon dioxide, ferric oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, orange flavour, povidone K 30, and sodium starch glycolate.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development
Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets are yellow coloured mottled, round shaped, beveled edged tablets with breakline and debossed with ‘M09’ on one side and plain on the other side.

The primary packs are round white aluminium sealed HDPE bottles fitted with PP continuous-thread closures and containing silica gel canister (pack size 60 tablets).

The development of the final composition of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg Dispersible Tablets has been described. The objective was to develop a fixed-dose combination dispersible tablet of Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg which is stable and bioequivalent to the following innovator products, taken concomitantly in suitable quantities: Epivir® oral solution (containing 10mg/ml of lamivudine), Viramune® oral suspension (containing 50mg/5ml of nevirapine as the hemihydrate) and Retrovir® syrup (containing 50mg/5ml of zidovudine). The qualitative formulation was developed and each of the excipients was selected for its intended use based on optimization studies. The manufacturing process employs both wet and dry granulation techniques in the manufacturing of the FPP. All the 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.

Validation data presented on three production batches, at the lower end of the proposed production range, demonstrated the consistency of the process and the quality of the product.

HPLC analytical methods were developed and validated for the determination of assay, related substances and for dissolution testing of the dispersible tablets. For release control and stability testing of FPP the specifications set by the manufacturer were judged suitable and justified, though the limits for loss on drying and related substances will be revisited by the manufacturer once sufficient batch release and stability data are available. The limits for disintegration, namely 3 minutes, and fineness of dispersion is in line with the Ph.Int. requirements.

Stability testing

Stability studies have been performed on the same three production batches used in the process validation studies at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions. The data showed little change with time. At the time of the prequalification, a provisional shelf-life of 24 months has been allowed for the FPP when stored at a temperature not above 30°C.

The applicant has committed to continue long-term testing on the current three production scale batches of the FPP for a period of time sufficient to cover the whole proposed shelf-life (24 months). The applicant has also committed to conduct process validation studies and long-term stability testing on production scale batches at the higher end of the proposed production range, according to agreed protocols.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Lamivudine plus Nevirapine plus Zidovudine 30/50/60mg tablets of Matrix Laboratories Limited, India (two tablets) and Epivir® Oral Solution containing 10mg/mL of Lamivudine of GlaxoSmithKline, USA (as 60mg dose), Viramune® Oral Suspension containing 50mg/5mL of Nevirapine (as nevirapine hemihydrate) of Boehringer Ingelheim Pharmaceuticals, Inc., USA (as 100mg dose) and Retrovir® Syrup containing 50mg/5mL of Zidovudine of GlaxoSmithKline, USA (as 120mg dose) in healthy adult human subjects, under fasting conditions (study no. 07-VIN-123).

The objective of the study was to compare the bioavailability of the stated lamivudine/nevirapine/ zidovudine 30/50/60 mg fixed dose combination dispersible tablet manufactured by Matrix Ltd., India (test drug) with the same dose of the individual reference formulations (Epivir and Retrovir, GlaxoSmithKline, and Viramune, Boehringer Ingelheim) and to assess bioequivalence. The comparison was performed as a randomized, open label, two treatment, two period, two sequence, single dose, 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 – Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg dispersible tablets 2 x (lamivudine 30mg/ nevirapine 50mg/ zidovudine 60 mg)
Batch no. 1001949.

Treatment R: Reference – Epivir® Oral Solution, 10mg/mL of lamivudine (GlaxoSmithKline, USA; 60mg dose)
Batch no. 6L016.

Reference – Viramune® Oral Suspension, 50mg/5mL of nevirapine (as nevirapine hemihydrate) (Boehringer Ingelheim Pharmaceuticals, Inc., USA; 100mg dose)
Batch no. 657813A.

Reference - Retrovir® Syrup 50mg/5mL of Zidovudine
(GlaxoSmithKline, USA; 120mg dose)
Batch no. 6M004

A wash-out period of at least 21 days was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 24 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 10 ng/ml for lamivudine, zidovudine and nevirapine.

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, 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)	0.879 ± 0.451	0.884 ± 0.303	-	-
C_{max} (ng/ml)	679.3± 211.3 (652.81)	643.8± 175.9 (620.3)	105.2	95.6 - 115.8
AUC_{0-t} (ng.h/ml)	2496.4± 692.8 (2408.7)	2536.457± 774.9 (2429.8)	99.13	91.5 - 107.3
AUC_{0-inf} (ng.h/ml)	2609.6± 704.3 (2521.8)	2646.9± 785.2 (2541.6)	99.22	91.9 - 107.1

* 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)	0.435 ± 0.18	0.405 ± 0.16	-	-
C_{max} (ng/ml)	786.2 ± 213.9 (756.1)	791.2± 277.8 (741.9)	101.9	92.6 - 112.1
AUC_{0-t} (ng.h/ml)	857.0 ± 168.7 (841.0)	847.5 ± 178.5 (829.7)	101.4	98.0 - 104.89
AUC_{0-inf} (ng.h/ml)	879.9± 168.8 (864.3)	868.8 ± 180.7 (851.0)	101.6	98.3 – 105.0

* 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)	2.38± 1.18	2.65 ± 1.20	-	-
C_{max} (ng/ml)	1305.2± 214.7 (1288.6)	1273.2± 173.4 (1261.2)	102.2	98.0 - 106.5
AUC_{0-72h} (ng.h/ml)	51147.6± 6779.6 (50708.8)	50866.1± 7644.4 (50295.9)	100.8	99.3% - 102.4

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine, zidovudine and nevirapine. Accordingly, the test tablet Lamivudine/Nevirapine/Zidovudine dispersible tablets 30/50/60mg meets the criteria for bioequivalence with regard to Epivir oral solution (GlaxoSmithKline, USA) Viramune oral suspension (Boehringer Ingelheim, USA) and Retrovir syrup (GlaxoSmithKline, USA).

4. Summary of Product Safety and Efficacy

[HA433 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual references Viramune oral suspension (Boehringer Ingelheim) and Retrovir syrup and Epivir oral solution (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 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

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 [HA433 trade name] is used in accordance with the conditions as stated in the SPC.

Bioequivalence

[HA433 trade name] has shown to be bioequivalent to the separate reference formulations Epivir oral solution Viramune oral suspension and Retrovir syrup.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA433 trade name] 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 assessment of data on quality and bioequivalence the team of assessors considered by consensus that the benefit risk profile of [HA433 trade name] was acceptable for the following indication: HIV infection in children weighing less than 25 kg, and has advised that the quality, efficacy and safety of [HA433 trade name] are acceptable to allow inclusion of [HA433 trade name], manufactured at Matrix Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik 422113, Maharashtra state, India in the list of prequalified medicinal products.