SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[HA426 trade name][*]
Manufacturer of Prequalified Product:	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C Sinnar 422113 Nashik Maharashtra India
Active Pharmaceutical Ingredients (APIs):	Lamivudine/Nevirapine/Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, nucleoside reverse transcriptase inhibitor, J05AR05
Therapeutic indication:	[HA426 trade name]is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and children weighing 25 kg or more.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.
[1] Formerly Matrix Laboratories Ltd

1. Introduction

[HA426 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and children that weigh at least 25 kg.

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 core tablet formulation include colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K-30 and sodium starch glycolate. TSE/BSE free certificates were provided for these excipients, which are compendial controlled. The film coating contains FD&C Blue # 2 Aluminium Lake, hypromellose, titanium dioxide and triacetin.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development
[HA426 trade name]are blue coloured, capsule shaped, biconvex, film coated tablets, debossed with "M" and "104" on one side and plain on the other side. The primary packs are PVC/PVDC-Al blister cards (10 tablets per blister card, 6 cards per carton) and round, wide mouth, white opaque, induction-sealed HDPE bottles fitted with a white opaque screw cap with induction sealing liner (60 tablets per bottle).

The development of the final composition of [HA426 trade name] has been described. The objective was to develop a stable, fixed dose combination, bioequivalent to the innovator products, Combivir 150mg/300mg Tablets and Viramune 200mg Tablets. The tablets have been developed as an immediate release solid dosage form for oral administration. Various experiments were performed to optimize the concentration of excipients and other process parameters to obtain coated tablets of desired characteristics. The manufacturing process employs both wet granulation (for nevirapine) and dry granulation techniques (for lamivudine and zidovudine). The granules are blended together, mixed with extra granulating agent and compressed. The compressed tablets are finally coated with the Opadry blue coating solution. 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 scale batches demonstrated the consistency of the process and the quality of the product.

The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.

Dissolution profile similarity of this multisource fixed-dose combination product has been demonstrated against the individual innovator FPPs, namely Combivir 150mg/300mg Tablets and Viramune 200mg tablets.

Stability testing
Stability studies have been performed on three production scale batches at the lower end of the production range, at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions. The data showed little change and were well within the agreed specifications at both storage conditions.
At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored at a temperature not above 30°C. The applicant committed to conduct process validation studies and long-term stability testing on production scale batches at the high 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 2006/2007 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of FDC tablet containing Lamivudine 150 mg + Zidovudine 300 mg + Nevirapine 200 mg of Matrix Laboratories Limited, India and Combivir® (Lamivudine 150 mg + Zidovudine 300 mg) tablet of Glaxo SmithKline Inc, USA + Viramune® (Nevirapine) 200 mg tablet of Boehringer Ingelheim Pharmaceuticals Inc., USA, in healthy human adult subjects, under fasting conditions (study no. 1078/06).

The objective of the study was to compare the bioavailability of the stated [HA426 trade name]manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the individual reference formulations (Combivir, Glaxo SmithKline, and Viramune, Boehringer Ingelheim Pharmaceuticals Inc) 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 – Lamivudine/zidovudine/nevirapine 150/300/200 mg tablet
(Lamivudine/zidovudine/nevirapine 150/300/200 mg)
Batch no. LNZA536001.
Treatment R: Reference – Combivir® tablet
(lamivudine/zidovudine 150/300 mg)
Batch no. 6ZP6939.
Reference – Viramune® tablet
(nevirapine 200 mg)
Batch no. 558027A.

A 21 day wash-out period 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 25 ng/ml for lamivudine and zidovudine and about 81 ng/ml for nevirapine.

The study was performed with 40 participants; data generated from a total of 36 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)	1.15 ± 0.51	1.22 ± 0.54	-	-
C_{max} (µg/ml)	1.76 ± 0.52 (1.69)	1.61 ± 0.48 (1.54)	110.0	101.7 – 119.0
AUC_{0-t} (µg.h/ml)	7.09 ± 1.46 (6.95)	6.65 ± 1.54 (6.47)	107.5	101.5 – 113.8
AUC_{0-inf} (µg.h/ml)	7.43 ± 1.48 (7.29)	6.98 ± 1.57 (6.80)	107.3	101.5 – 113.4

* 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)	0.64 ± 0.41	0.65 ± 0.45	-	-
C_{max} (µg/ml)	1.85 ± 0.82 (1.68)	1.88 ± 0.79 (1.70)	99.2	81.5 – 120.6
AUC_{0-t} (µg.h/ml)	2.74 ± 0.63 (2.67)	2.79 ± 0.64 (2.71)	98.3	91.9 – 105.1
AUC_{0-inf} (µg.h/ml)	2.82 ± 0.64 (2.75)	2.87 ± 0.63 (2.80)	98.2	92.0 – 104.8

* 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)	5.40 ± 6.10	4.13 ± 5.58	-	-
C_{max} (µg/ml)	2.40 ± 0.45 (2.36)	2.48 ± 0.43 (2.44)	96.6	93.4 – 100.0
AUC_{0-72h} (µg.h/ml)	111 ± 17 (110)	112 ± 16 (111)	99.6	97.9 – 101.3

* 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 fixed dose combination [HA426 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Combivir® (Glaxo SmithKline) and Viramune® (Boehringer Ingelheim Pharmaceuticals).

Summary of Product Safety and Efficacy

[HA426 trade name]have 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 Combivir® (GlaxoSmithKline) and Viramune (Boehringer Ingelheim Pharmaceuticals), 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

[HA426 trade name] has shown to be bioequivalent to the separate reference formulations Combivir® (GlaxoSmithKline) and Viramune (Boehringer Ingelheim Pharmaceuticals).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA426 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 [HA426 trade name] was acceptable for the indication "HIV infection" and has advised to include [HA426 trade name], manufactured at Matrix Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, 422113 Nashik, Maharashtra, India, in the list of prequalified medicinal products.