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	[HA403 trade name]*
Manufacturer of Prequalified Product	Matrix Laboratories Limited 1-1-151/1, 5th Floor Sairam Towers Alexander Road 500 003 Secunderabad India
Active Pharmaceutical Ingredient (API)	Efavirenz
Pharmaco-therapeutic group (ATC Code)	Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitor (J05AG03)
Therapeutic indication:	[HA403 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents.

1. Introduction

[HA403 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral agents in adults and adolescents.

[HA403 trade name] 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)

Efavirenz is a class 4/2 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).*

Data provided in the dossier show that efavirenz is practically insoluble in aqueous medium over the pH range 1.2 to 8.0.
Efavirenz is manufactured in a two-step process from a commercially available starting material. Efavirenz can exist in five crystalline forms (Forms I, II, III, IV and V). The crystalline forms were characterised by X-ray powder diffraction and DSC. Form I is consistently produced.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
†Formerly known as Matrix Laboratories Limited

Efavirenz API is described in the Ph.Int. However, by the time of submission of the dossier the monograph was not yet included in the Ph.Int. The proposed specifications, which include particle size distribution and enatiomeric purity, were justified and considered suitable for control of the API. Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months was approved for efavirenz.

Other ingredients

Other ingredients used in the tablet core formulation include croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. Magnesium stearate is of vegetable origin. The film coating contains hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol 400 and titanium dioxide.

Finished pharmaceutical product (FPP)

Presentation

Efavirenz 600mg Tablets are peach coloured, capsule shaped film-coated tablets, debossed with "M109" on one side and plain on other side. The primary packs are clear transparent PVdC-coated PVC/aluminium blister cards and white, opaque HDPE bottles fitted with polypropylene child-resistant cap.

Pharmaceutical development

The development of the final composition of Efavirenz 600 mg Tablets has been described. The objective of the pharmaceutical development was to obtain a stable tablet formulation, essentially similar in composition and bioequivalent to the innovator product, Sustiva 600 mg Tablets. The qualitative formulation was developed and each of the excipients was selected for its intended use based on optimization studies. Micronised efavirenz showed poor flow properties.

Acceptable flow properties were achieved by applying a wet granulation method. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three production scale batches demonstrated the consistency of the process. The proposed specifications are regarded adequate for ensuring consistent quality of this FPP.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term conditions and at accelerated conditions. At the time of the prequalification, a provisional shelf-life of 24 months has been allowed for the FPP when stored not above 30°C in the original container. The applicant committed to continue long-term testing on production scale batches for a period of time sufficient to cover the whole proposed shelf-life and to report any out-of-specification results immediately to WHO.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2006 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Efavirenz 600 mg tablets of Matrix Laboratories Limited, India and Sustiva® (Efavirenz) 600 mg tablets of Bristol-Myers Squibb Co., NJ, USA, in healthy human adult subjects, under fasting conditions (study no. 1022/06).

The objective of the study was to compare the bioavailability of the stated Efavirenz 600 mg tablets manufactured by Matrix Laboratories Limited, India (test drug) with the same dose of the reference tablet (Sustiva, Bristol-Myers Squibb) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – Efavirenz 600 mg tablets (efavirenz 600 mg) Batch no. EFZA536001.
Treatment R: Reference – Sustiva® tablet (efavirenz 600 mg) Batch no. EUA120A.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 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 efavirenz were analyzed using a validated HPLC-UV method. The limit of quantification was stated to be about 72 ng/mL for efavirenz.

The study was performed with 30 participants; data generated from a total of 26 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for efavirenz as well as statistical results are summarised in the following table:

Efavirenz

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)	3.52 ± 1.31	3.87 ± 1.52	-	-
C_{max} (µg/mL)	3.2 ± 0.82 (3.1)	2.93 ± 0.78 (2.81)	109.4	99.1 – 120.8
AUC_{0-72h} (µg.h/mL)	82.78 ± 22.95 (80.14)	78.47 ± 22.69 (75.00)	106.9	99.9 – 114.2

* 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 efavirenz. Accordingly, the test product [HA403 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Sustiva® (Bristol-Myers Squibb).

4. Summary of Product Safety and Efficacy

[HA403 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [HA403 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Sustiva, 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 considered. 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 [HA403 trade name] is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

[HA403 trade name] has shown to be bioequivalent to the reference formulation Sustiva (Bristol-Myers Squibb).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA403 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on WHO's assessment of data on quality and bioequivalence the team of assessors considered that the benefit-risk profile of [HA403 trade name] was acceptable for the following indication: "for the treatment of HIV-1 infected adults and adolescents (weighing 40 kg or more) in combination with other antiretroviral agents" and has advised that the quality, efficacy and safety of [HA403 trade name] are acceptable to allow inclusion of [HA403 trade name], manufactured at Matrix Laboratories Limited, Sairam Towers, Alexander Road, 500 003 Secunderabad, India in the list of prequalified medicinal products.