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	[HA633 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited Plot No: S-155 to S-159 & N1 Phase III & Phase IV Verna Industrial Estate Verna Goa–403722 India
Active Pharmaceutical Ingredient (API)	Efavirenz
Pharmaco-therapeutic group (ATC Code)	Non-nucleoside reverse transcriptase inhibitor (J05AG03)
Therapeutic indication	[HA633 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

1. Introduction

[HA633 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.

[HA633 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 Ingredient (API)

Data provided in the dossier show that efavirenz is of BCS low solubility across the physiological pH range, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. Efavirenz can exist in several crystalline forms; form I, characterized X-ray powder diffraction (XRPD), is consistently produced. The acceptance criteria for PSD were set on information of the API lot related to the FPP biobatch.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and UV), water content (KF), residue on ignition, specific optical rotation, heavy metals, completeness of solution, organic impurities (HPLC), assay (HPLC), enantiomer content (chiral HPLC; ≤ 0.15%), polymorphic form (XRPD), residual solvents (GC), PSD (laser diffraction) and determination of metal impurities (ICP-MS).

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

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate, hydroxypropyl cellulose, microcrystalline cellulose and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, iron oxide yellow, macrogol/PEG and titanium dioxide. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, capsule shaped, biconvex, film coated tablet, debossed "O" on one side and plain on the other side. The tablets are packaged in PVC/PVDC-aluminium blister cards and in opaque white HDPE bottles with polypropylene child resistant caps.
The development of the final composition of the multisource product has been described. The aim was to develop a stable immediate release tablet dosage form which would be pharmaceutically equivalent and bioequivalent to the WHO recommended comparator product,
Sustiva® Tablets 600 mg. The comparator product was characterized in support of the development. The excipients selected for the core tablets are qualitatively similar to those present in the comparator product. Among the critical quality attributes of the API considered, it was concluded that solubility and particle size have high an impact on dissolution profile.
Due to poor flow properties of efavirenz and the high API content in the formulation, a conventional wet granulation process was selected for manufacturing the tablets. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality and include tests for description, identification of the API (HPLC and UV), average and uniformity of weight, disintegration time, tablet dimensions, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), enantiomeric purity of the API (chiral HPLC), residual solvents (GC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies on the FPP have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable at both these storage conditions in the pack types proposed for marketing of the product. 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.

Study title: A randomized, open label, balanced, two-sequence, two-treatment, two-period, single dose, crossover bioequivalence study of [HA633 trade name] of Micro Labs Ltd., with Sustiva® (efavirenz) tablets 600 mg of Bristol-Myers Squibb Company, USA, in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/10/228).

The objective of the study was to compare the bioavailability of the stated [HA633 trade name] manufactured for/by Micro Labs. Ltd., India (test drug) with the reference formulation Sustiva®

(Bristol-Myers Squibb Company) 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 treatments in a randomized fashion:

Treatment T: Test – 1 tablet [HA633 trade name]
(efavirenz 600 mg) Batch no. EZAG002
Treatment R: Reference – 1 tablet Sustiva®
(efavirenz 600 mg)
Batch no. 8E41826A

A 24 day wash-out period was observed between administration of test and reference. 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 efavirenz were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for efavirenz.

The study was performed with 46 participants; data generated from a total of 40 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.11 ± 1.00	3.25 ± 1.15	–	–
C_{max} (ng/mL)	3267 ± 1014 (3065)	3093 ± 1084 (2900)	105.7	96.3 – 116.0
$AUC_{0\text{-}72h}$ (ng·h/mL)	62621 ± 22369 (58517)	60542 ± 15883 (58474)	100.0	93.2 – 107.5

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 [HA633 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Sustiva® (Bristol-Myers Squibb Company).

4. Summary of product safety and efficacy

[HA633 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, [HA633 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sustiva® tablets 600 mg (Bristol-Myers Squibb Company, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA633 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 [HA633 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA633 trade name] has been shown to be bioequivalent with Sustiva® tablets 600 mg (Bristol – Myers Squibb, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA633 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 [HA633 trade name] was acceptable for the following indication: 'for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents', and would allow inclusion of [HA633 trade name], manufactured at Micro Labs Limited, Plot No: S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa–403722, India in the list of prequalified medicinal products.