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:	[HA390 trade name][*]
Manufacturer of Prequalified Product:	Strides Pharma Science Limited 36/7, Suragajakkanahalli Indlavadi Cross, Anekal Taluk Bangalore Karnataka – 562 106 India. And Universal Corporation Limited. Club road, past Kikuyu post office, Plot no. 13777 P.O. Box: 1748-00902, Kikuyu, Kenya.
Active Pharmaceutical Ingredient (API):	Efavirenz
Pharmaco-therapeutic group (ATC Code):	Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitor (J05AG03)
Therapeutic indication:	[HA390 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents.

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

1. Introduction

[HA390 trade name] is indicated for the treatment of infected adults and adolescents weighing 40 kg or more who are infected with human immunodeficiency virus type 1 (HIV-1).

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)

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.

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 enantiomeric 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 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 black, iron oxide red, iron oxide yellow, polyethylene glycol 400 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The development of the final composition of [HA390 trade name] has been described. Excipients were selected based on the composition of the innovator product, Sustiva® 600mg film-coated tablets. In the developmental studies several trials were conducted using variable quantities of excipients to obtain a formulation comparable to Sustiva® in terms of physico-chemical properties, including dissolution profile similarity in different media. Based on these studies, a prototype formulation was selected as the product formulation. The developmental data is considered satisfactory.

The manufacture of the tablets involves wet granulation. 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/65%RH (zone IVa) as long-term conditions and at accelerated conditions. No negative trend was reported. 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, protected from light. The manufacturer committed to continue long-term testing for

a period of time sufficient to cover the full provisional shelf life of 24 months and to report any out-of-specification results or significant changes 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, cross-over, bioequivalence study of [HA390 trade name] of Strides Pharma Science Limited, India, and Sustiva® (efavirenz) Tablets 600 mg (study no. 833/06).

The objective of the study was to compare the bioavailability of the stated [HA390 trade name] manufactured by Strides Pharma Science Ltd., India (test drug) with the same dose of the reference formulation (Sustiva, Bristol-Myers Squibb) 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 – Efavirenz 600 mg tablet (efavirenz 600 mg) Batch no. 7201893.

Treatment R: Reference – Sustiva® 600 mg tablet (efavirenz 600 mg) Batch no. ETH445A.

A 30 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 21 samples within 504 hours 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 method. The limit of quantification was stated to be about 72 ng/mL for efavirenz.

The study was performed with 36 participants; data generated from a total of 32 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)	3.98 ± 2.48	3.84 ± 0.94	-	-
C_{max} (µg/mL)	2.40 ± 0.67 (2.31)	2.70 ± 0.97 (2.56)	90.0	80.4 – 101.8
AUC_{0-t} (µg.h/mL)	120 ± 35 (115)	127 ± 41 (121)	95.5	89.8 – 102.6
AUC_{0-inf} (µg.h/mL)	138 ± 37 (133)	145 ± 45 (138)	95.9	90.7 – 102.0

* 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 tablet Efavirenz 600 mg 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

[HA390 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, [HA390 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sustiva, for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA390 trade name] is considered acceptable when guidance and restrictions as 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 [HA390 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA390 trade name] has been shown to be bioequivalent with Sustiva® 600 mg tablet (Bristol-Myers Squibb, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA390 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 [HA390 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 would allow inclusion of [HA390 trade name], manufactured at Strides Pharma Science Limited, Anekal Taluk, 562 106 Bangalore, Karnataka, India in the list of prequalified medicinal products.