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	[HA681 trade name]*
Manufacturer of Prequalified Product	The Government Pharmaceutical Organization Rangsit Pharmaceutical Production Plant 1 138 Moo 4, Rangsit-Nakhonnayok Road Bueng Sanan Thanyaburi Pathumthani 12110 Thailand
Active Pharmaceutical Ingredient (API)	Efavirenz
Pharmaco-therapeutic group (ATC Code)	Non-nucleoside reverse transcriptase inhibitor (J05AG03)
Therapeutic indication	[HA681trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

1. Introduction

[HA681 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official treatment guidelines (e.g. those by WHO).

[HA681 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)

Efavirenz has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of Efavirenz 600mg tablets, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Based on the low aqueous solubility profile of Efavirenz API across the physiological pH range, particle size distribution (PSD) and polymorphism were considered to be critical API quality

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

parameters for the FPP manufacturer. PSD limits and polymorphic form were set on the data obtained for the API batch used in the manufacture of the biobatch.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulphate, lactose monohydrate and magnesium stearate. Magnesium stearate is from plant origin. A TSE/BSE free attestation has been provided for lactose monohydrate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/polyethylene glycol, iron oxide yellow and iron oxide red.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a peach coloured, oblong, biconvex, one side "EZ 600" marked and plain on other side, film-coated tablet. The tablets are packed in a white high-density polyethylene (HDPE) bottle with narrow screw neck with aluminium foil and fitted with a white plastic HDPE screw closure with Hi-sheet liner. A desiccant comprised of a plastic bag with perforation for breathing containing silica gel beads is included in each bottle.

The aim of the development was to formulate a solid oral immediate release tablet dosage form containing 600 mg efavirenz per tablet based on information of the WHO recommended comparator product, Sustiva® Tablets 600 mg. The composition of the core tablet is qualitatively identical to the WHO recommended comparator product. Due to the poor flow properties of the API and to obtain good compressibility of the granulate, wet granulation was selected as the method of manufacture of the core tablets. The critical steps of the manufacturing process have been optimized. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, identification (HPLC, UV), dissolution, uniformity of dosage units (by weight variation), assay, organic impurities, water content and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product was shown to have good stability in the packaging configuration at the storage conditions. 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 2016 according to internationally accepted guidelines.

A randomized, open label two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of efavirenz formulations, Efavirenz 600 mg tablets of The Government Pharmaceutical Organization (GPO), Thailand and Sustiva® (efavirenz) 600 mg tablets of Bristol-Myers Squibb, Princeton, NJ 08543 USA in healthy, adult, human subjects under fasting conditions (study no. 821-15).

The objective of the study was to compare the bioavailability of the stated Efavirenz 600 mg tablet manufactured by/for The Government Pharmaceutical Organization, Thailand (test drug) with 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 subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Efavirenz 600 mg (efavirenz 600 mg) Batch no. S595004.
Treatment R:	Reference – 1 tablet Sustiva® (efavirenz 600 mg) Batch no. AAC8153A.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 72 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 LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for efavirenz.

The study was performed with 42 participants; data generated from a total of 35 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)#	4.0 (1.5-7.0)	3.7 (2.0-6.0)	-	-
C_{max} (ng/mL)	3085 ± 622 (3021)	2801 ± 897 (2670)	113.2	105.3 – 121.7
AUC_{0-72h} (ng·h/mL)	66498 ± 19700 (63895)	60654 ± 19770 (58127)	109.9	105.7 – 114.3

#median (range)

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding efavirenz. Accordingly, the test Efavirenz 600 mg tablet 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).

4. Summary of Product Safety and Efficacy

[HA681 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, [HA681 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sustiva® tablets 600 mg for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of [HA681 trade name] is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. 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 [HA681 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA681 trade name] has shown to be bioequivalent with Sustiva® tablets 600 mg (Bristol-Myers Squibb, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA681 trade name] is considered effective and safe to use when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA681 trade name] was acceptable for the following indication: " in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents" and would allow inclusion of [Ha681 trade name], manufactured at The Government Pharmaceutical Organization, Rangsit Pharmaceutical Production Plant 1, 138 Moo 4, Rangsit-Nakhonnayok Road, Bueng Sanan, Thanyaburi, Pathumthani 12110, Thailand, in the list of prequalified medicinal products.