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	[HA352 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited Mumbai Central Mumbai 400 008, India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz
Pharmaco-therapeutic group (ATC Code)	Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitor (J05AG03)
Therapeutic indication	[HA352 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents.

1. Introduction

[HA352 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*).

Efavirenz API is described in the Ph.Int.

Data provided 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. The proposed specifications 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.

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

Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, magnesium stearate, povidone, pregelatinised starch and sodium starch glycolate, with Opadry 03B52570 yellow as coating material.

Finished pharmaceutical product (FPP)

Presentation

[HA352 trade name] is yellow coloured, capsule shaped, biconvex film-coated tablets debossed with 'EFV' on one side and plain on the other side. The tablets are packaged in cylindrical, white opaque HDPE bottles fitted with screw caps and containing a desiccant (pack size: 30 *tablets).*

Pharmaceutical development and manufacture

The description of the steps taken to design the dosage form is provided. The development is based on the amount of drug substance to be administered and its ratio in the formulation. Efavirenz is practically insoluble in water (< 10µg/ml), and the studies undertaken to optimise the chosen particle size distribution thereof for incorporation into the FPP has been described. Direct compression was discounted in favour of wet granulation because the formulation is high dose and in order to obtain a formulation with a more appropriate dissolution rate for a poorly water soluble drug. The manufacturing process is conventional: mixing, granulation, drying/sizing, lubrication, compression and coating. The tablets showed dissolution profiles similar to that of the innovator product, Sustiva 600 mg film-coated tablets.

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 on three production scale batches at 25C/60%RH and 30C/65%RH as long-term conditions and for six months at accelerated conditions. At the time of the prequalification shelf-life of 24 months has been allowed for the FPP when stored not above 30°C in the original container.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

A randomized, single dose, open label, two-period, two-treatment, two sequence crossover bioequivalence study comparing [HA352 trade name] (manufactured by Cipla Limited, Goa, India) and Sustiva® (efavirenz) tablets 600 mg (distributed by: Bristol-Myers Squibb, Princeton, NJ 08543, USA) in 28 + 2 standbys normal healthy male subjects in fasting condition (study no. US/05/007).

The objective of the study was to compare the bioavailability of the stated [HA352 trade name] manufactured by Cipla Ltd., 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 – [HA352 trade name](efavirenz 600 mg)
Batch no. G56848.

Treatment R: Reference – Sustiva® tablet (efavirenz 600 mg)
Batch no. ETA053A.

A 21 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 336 h post dose) were taken during each study period to obtain the 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 for efavirenz was stated to be 50 ng/mL.

The study was performed with 30 participants; data generated from a total of 28 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)	3.22 ± 1.19	3.36 ± 1.22	–	–
C_{max} (µg/mL)	2.80 ± 1.33 (2.51)	2.63 ± 1.22 (2.47)	106.7	85.3 – 120.5
AUC_{0-t} (µg·h/mL)	105 ± 48 (94)	110 ± 47 (101)	95.1	82.7 – 106.3
AUC_{0-inf} (µg·h/mL)	115 ± 51 (105)	121 ± 50 (111)	95.0	83.7 – 105.9

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 [HA352 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

[HA352 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 [HA352 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 [HA352 trade name] is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made to the SPC (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 [HA352 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA352 trade name] has been shown to be bioequivalent with the reference formulation Sustiva (Bristol-Myers Squibb, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA352 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 [HA352 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 [HA352 trade name] are acceptable to allow inclusion of [HA352 trade name], manufactured at Cipla Ltd, Goa, India in the list of prequalified medicinal products.