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	[HA306 trade name]*
Manufacturer of Prequalified Product	Ranbaxy Laboratories Limited, India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz
Pharmaco-therapeutic group (ATC Code)	Antiviral for systemic use, non-nucleoside reversee transcriptase inhibitor (J05A G03)
Therapeutic indication	[HA306 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

[HA306 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA306 trade name] is not indicated for use in patients with clinically significant hypersensitivity to efavirenz or any of the components contained in the formulation.

It is recommended that therapy is given only on the advice of an HIV experienced physician.

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)

The critical process parameters were defined in the synthesis of efavirenz and they are routinely monitored. A detailed purification procedure was presented.

By the time of the submission / assessment of the dossier a monograph for efavirenz was not included in any major pharmacopoeia for control of the API. The set of efavirenz specifications as set by the FPP manufacturer was judged suitable. Polymorphic Form 1 is consistently produced.

All excipients are official in major international pharmacopoeias and are commonly used in the manufacture of capsules.

Stability studies have confirmed the already-known good solid state stability of efavirenz. A provisional two (2) years retest period is pre-qualified by WHO. The applicant undertook in writing to continue long-term testing of efavirenz for a period of time sufficient to cover the whole proposed retest date (NLT 24 months) and to report any out-of-specification results immediately to WHO.

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

Other ingredients

The other ingredients of [HA306 trade name] are microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium laurylsulphate, lactose monohydrate, magnesium stearate, hypromellose, titanium dioxide, PEG400, iron oxide yellow and iron oxide red.

A Ph.Eur. TSE certificate of suitability was provided for the magnesium stearate provided by the stated manufacturer. Microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium laurylsulphate, lactose monohydrate and magnesium stearate are included in USP, Eur.Ph as well as the commercial film coating material containing hypromellose, titanium dioxide, PEG400, iron oxide yellow and iron oxide red.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA306 trade name] is peach coloured, capsule shaped, biconvex, film-coated tablets, debossed with "RC68" on one side and plain on the other side. The tablets are packaged in white opaque HDPE bottles having screw caps or with child resistant closures (30 tablets) and alu/alu blister packs (10 tablets).

The primary packs are (1) white opaque HDPE bottles having screw caps or with child resistant closures (30 tablets) and (2) alu/alu blister packs (10 tablets).

The development of the final composition has been described. Critical process variables were optimized during the pharmaceutical R&D stage.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three production scale batches demonstrated the consistency of the process and the quality of the product.

Stability testing

Data on accelerated and real time stability data were presented for three production scale batches of [HA306 trade name] in the marketed containers. Both the accelerated (40°C/75%RH) and climatic zone II (25°C/60%RH) and climatic zone IV (30°C/70%RH) long-term stability data showed so little degradation and so little variability that it was apparent from looking at the data that it was normally unnecessary to go through the formal statistical analysis.

A provisional shelf life of two (2) years has been pre-qualified by WHO. The Applicant undertook in writing to continue long-term testing of [HA306 trade name] for a period of time sufficient to cover the whole proposed retest date (NLT 24 months) 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 2005 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioavailability study on efavirenz 600 mg formulation comparing [HA306 trade name] of Ranbaxy Laboratories with Sustiva 600 mg tablets (containing efavirenz 600 mg) of Bristol-Myers Squibb, USA, in healthy, adult human subjects under fasting conditions (study number 001/EFAVI-600/05).

The objective of the study was to compare the bioavailability of the stated 600 mg efavirenz formulation manufactured by Ranbaxy Laboratories Limited, India (test drug) with the same dose of the reference and to assess bioequivalence. The comparison was performed as a single centre,

crossover study in healthy subjects. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – [HA306 trade name]
(efavirenz 600 mg, Ranbaxy Laboratories, India)
Batch No. 1477548
Treatment R: Reference – Sustiva 600 mg tablet
(efavirenz 600 mg, Bristol-Myers Squibb, USA)
Batch No. ESD158A

A 35 day wash-out period was observed between administration of test and reference. Serial blood samples (1 predose sample and 23 samples up to 96 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Additional information was obtained for plasma concentrations obtained at 12 h postdose and 24 h post-dose (C_{12h} and C_{24h}, respectively). Drug concentrations for efavirenz in plasma were analyzed using a validated LC-MS/MS method. Limit of quantification was stated to be 10 ng/mL for efavirenz.

The study was performed with 40 volunteers, however three subjects dropped out during one of the study periods, and for one subject not all relevant plasma concentrations could be obtained due to missing samples. Accordingly, data generated from 36 participating subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (AUC, C_{max}, t_{max}), geometric means (AUC, C_{max}) and 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)	3.5 ± 1.0	3.5 ± 1.2	–	–
C_{max} (ng/mL)	3604 ± 1012 (3604)	3131 ± 1381 (3119)	120	108-133
AUC_{0-96h} (ng·h/mL)	88075 ± 3604 (87819)	81994 ± 30083 (81627)	109	103 – 115

The results of the study show that preset acceptance limits of 80 -125 % are met by AUC, and for C_{max} the wider acceptance range of 75 – 133% was met. Additional data were provided to support the wider acceptance limits. In addition, C_{12h} and C_{24h} were inside the 80 – 125% limits (C_{12h}: ratio 107.1, 90% CI 96.6 – 118.7; C_{24h}: ratio 107.5, 90% CI 101.5 – 113.8%). Accordingly, the test product Ranbaxy [HA306 trade name] is considered bioequivalent to the reference Sustiva 600 mg tablets.

4. Summary of product safety and efficacy

[HA306 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, [HA306 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Sustiva, for which benefits have been proven in terms of clinical efficacy.

Product Design.

The development strategy for [HA306 trade name] focused on the compatibility of the active ingredient with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Unique Product Characteristics

[HA306 trade name] is peach coloured, capsule shaped, biconvex, film coated tablets, debossed with "RC68" on one side and plain on the other side.

Approved Indication

[HA306 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by efavirenz.

Pharmacokinetics

Absorption and Bioavailability

Oral bioavailability is 40% to 45% without food. Fat-containing meals increase absorption significantly.

Peak efavirenz plasma concentrations of 1.6 - 9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose related increases in Cmax and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

In HIV infected patients at steady state, mean Cmax, mean Cmin, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state Cmax was 12.9 ± 3.7 µM (29%) [mean ± S.D. (% C.V.)], steady state Cmin was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM·h (40%).

Distribution

Efavirenz is highly bound (approximately 99.5 - 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism / Elimination

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200 - 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42% lower) and a shorter terminal half-life of 40 - 55 hours (single dose half-life 52 - 76 hours). Approximately 14 - 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Drug Interactions, related side effects and contraindications.

Efavirenz is contraindicated in patients with clinically significant hypersensitivity to efavirenz or to any of the components contained in the formulation.

Efavirenz is an inducer of the hepatic enzyme CYP3A4 and an inhibitor of some CYP isozymes including CYP4A; therefore, it is possible that co-administration of efavirenz with medicinal products (for example astemizole, terfenadine, cisapride, midazolam, triazolam, ergot derivatives and St. John's wort) or food (for example, grapefruit juice) which affect CYP3A4 activity may result in an alteration in the plasma concentration of either agent.

Efavirenz decreases plasma concentrations of methadone (*1*). Methadone-maintained patients beginning efavirenz therapy should be assessed for evidence of withdrawal and methadone dose should be adjusted accordingly.

Rifampicin may significantly decrease levels of efavirenz (*2*). Rifampin levels are unaffected.

Efavirenz decreases serum levels of atorvastatin, pravastatin and simvastatin (*3*).

Efavirenz decreases serum levels of clarithromycin and increases the risk of rash significantly.

Efavirenz increases levels of ethinyl estradiol. Barrier contraception should always be used in combination with other contraceptive methods.

Efavirenz significantly decreases levels of amprenavir, atazanavir, indinavir, lopinavir, and saquinavir but increases levels of nelfinavir and ritonavir. Therefore, if efavirenz is given with either of these drugs, dosage adjustments of either may be necessary or alternatively ritonavir boosting may be necessary. Efavirenz does not alter the levels of fosamprenavir or tipranavir. Ritonavir significantly increases levels of efavirenz.

Clinical Efficacy

Efavirenz has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs (*4-15*). These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with other nucleoside analogue(s) and/or a PI. In recent studies by intention-to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/mL after 48 weeks of combination treatment that included efavirenz with other antiretroviral drugs (*5, 15*).

HIV-1 resistance to efavirenz involves the development of mutations in the reverse transcriptase gene at positions 100, 103, 106, 108, 181, 188 and 190 (www.iasusa.org). The K103N or Y188L mutation alone prevents the clinical utility of efavirenz. The V106M mutation is more common in HIV-1 subtype C than subtype B.

Rapid emergence of resistance to NNRTIs, including efavirenz, is likely to occur in case of virological failure.

Patients who are infected with known efavirenz-resistant HIV or patients who have previously experienced virological failure on a efavirenz- or nevirapine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing efavirenz or nevirapine.

Clinical studies in special populations

Liver Disease
No dose adjustment is necessary for mild to moderate liver impairment but discontinuation may be necessary for severe liver impairment.

Renal Impairment
No dose modification (*16, 17*).

Clinical Safety

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV infection with efavirenz.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Metabolic and nutrition disorders:
Very common: Increases in fasting triglycerides, total cholesterol, high- and low-density lipoprotein cholesterol (*18, 19*).
Common: Gynaecomastia (*20*).

Nervous system disorders
Very common: headache, confusion, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming (*4, 21*).
Common: Anxiety and depression (*8*) .
Uncommon: Psychosis (increased likelihood in those with history of psychiatric disease).

Hepatobiliary disorders
Common: Elevation of liver enzymes (*22, 23*).

Skin and subcutaneous tissue disorders
Very common: Rash (*4, 8, 24*).

General disorders
Very common: fatigue

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

5. Benefit risk assessment and overall conclusion

Quality

The quality of [HA306 trade name] is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Stability studies have been conducted on three production scale batches of [HA306 trade name] stored at 25°C/60±5%RH (6-month), 30°C/65±5%RH (6-month) and 40°C/75±5%RH (6-month). Based on these results a provisional shelf life of 24 months was prequalified on condition that further results on long term testing of ongoing stability studies are submitted.

Stability results show that [HA306 trade name] conform with the proposed end of shelf life specification including description, disintegration time, dissolution, assay and degradation products.

Bioequivalence

[HA306 trade name] has shown to be bioequivalent to comparator product, Sustiva® 600 mg tablets.

Efficacy and Safety

Regarding clinical efficacy and safety, efavirenz is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics is 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 [HA306 trade name] was acceptable for the following indication: **HIV infection in combination with other antiretroviral agents** and has advised to include [HA306 trade name], manufactured at Ranbaxy Laboratories Limited, Paonta Sahib, District Sirmour, Himachal Pardesh – 173025, India, in the list of pre-qualified medicinal products.

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