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	[HA200 trade name]*
Manufacturer of Prequalified Product	Cipla Limited Mumbai Central Mumbai 400 008 India
Active Pharmaceutical Ingredient(s) (API)	Nevirapine
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitor (J05A G01)
Therapeutic indication	Nevirapine 50 mg/5 mL oral suspension is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. It is also indicated for prevention of maternal-fetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants.

1. Introduction

[HA200 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents for children weighing up to 25 kg. It is also indicated for prevention of maternal-fetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants. Nevirapine oral suspension is not indicated for use in patients with clinically significant hypersensitivity to nevirapine or to 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)

Nevirapine is a weak base class 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).

Nevirapine exists in two crystal forms: the anhydrous form and the hemihydrate. Hemihydrate nevirapine is used in the manufacture of nevirapine 50 mg/5 mL oral suspension. The active pharmaceutical ingredient is described in the Ph.Int. and the USP. The API, which is obtained from an approved API manufacturer, is adequately controlled by its set of pharmacopoeial-based quality specifications, with additional in-house specifications including residual solvents and particle size.

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

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months was approved for nevirapine hemihydrate, when stored not above 30°C.

Other ingredients

Other ingredients used in the oral suspension include methyl parahydroxybenzoate, microcrystalline cellulose, polysorbate 80, propyl parahydroxybenzoate, purified water, simethicone emulsion, sodium saccharin and sorbitol solution 70%.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA200 trade name] is a white to off-white uniform suspension. The suspension is filled in 100-mL amber-coloured PET bottle, 25-mL amber-coloured glass bottle and 10-mL amber-coloured glass bottle together with plastic pouch containing a plastic cannula and a 2-mL dosing syringe with a dust cap. The 100-mL and 25-mL bottle packs also include a 10-mL measuring cup. The Ph.Int. monograph for nevirapine oral suspension has been adopted by WHO's Expert Committee on Specifications for Pharmaceutical Preparations for addition to the Fourth edition of the Ph.Int., Second Supplement. Nevirapine oral suspension is also included in the USP. The description of the steps taken to design the dosage form has been provided. The manufacturing process of the FPP is standard for an oral suspension and has been adequately described. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Process validation data, including the filling process, presented for three production scale batches demonstrated the consistency of the quality of the product. The accuracy and precision of different single doses recommended in the SPC and PIL have been demonstrated using the 2-mL dosing syringe and a test for uniformity of mass of delivered doses using the syringe for 0.2 mL, 1 mL and 2 mL is included in the FPP specifications. The proposed FPP specifications are regarded adequate for ensuring consistent quality of this oral suspension.

Stability testing

Stability studies have been performed on three production scale batches at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. The product showed good stability: chemically, physically (including sedimentation rate and redispersibility) and microbiologically. At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored not above 30°C. The oral suspension should be used within one month from the date of first opening.

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, single-centre single-dose, open-label, parallel-design bioequivalence study of [HA200 trade name] in normal healthy male subjects under fasting condition (study No. WH/AHD/06/002). The objective of the study was to compare the bioavailability of the stated [HA200 trade name] manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Viramune 50 mg/5 mL oral suspension, Boehringer Ingelheim) and to assess bioequivalence. Each subject was assigned to receive one of the following two treatments:

Treatment T: Test – 10 mL [HA200 trade name]
(nevirapine 50 mg/5 mL oral suspension)
Batch No. G50426.

Treatment R: Reference – 10 mL Viramune® 50 mg/5 mL oral suspension
(nevirapine 50 mg/5 mL)
Batch No. 556069E.

Serial blood samples (1 pre-dose sample and 25 samples within 72 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 nevirapine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/mL for nevirapine. The study was performed with 36 participants; data generated from a total of 36 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence. Arithmetic mean and geometric mean values of the pharmacokinetic variables for nevirapine as well as statistical results are summarised in the following table:

Nevirapine

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)	2.17 ± 0.87	2.82 ± 1.18	–	–
C_{max} (ng/mL)	1473 ± 281 (1447)	1355 ± 267 (1334)	108.5	97.6 – 120.6
AUC_{0-t} ng·h/mL)	53388 ± 10821 (52328)	50071 ± 7173 (49589)	105.5	95.4 – 116.7

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and C_{max} values regarding nevirapine. Accordingly, the test product [HA200 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Viramune® (Boehringer Ingelheim Pharmaceuticals).

4. Summary of product safety and efficacy

[HA200 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference, Viramune® 50 mg/5 mL oral suspension. The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA200 trade name] has shown to be bioequivalent with Viramune® 50 mg/5 mL oral suspension (Boehringer Ingelheim Pharmaceuticals Inc, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA200 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [HA200 trade name] was acceptable for the following indication: "HIV-1 infection in combination with other antiretroviral agents and prevention of maternal-fetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants" and has advised to include HA200 trade name], manufactured at Cipla Limited, LBS Marg, Vikhroli Mumbai 400 083, Maharashtra state, India, in the list of prequalified medicinal products.