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	[HA567 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited Plot No: S-155 to S-159 & N1, Phase III & IV Verna Industrial Estate, Verna, Salcette, Goa - 403722 India
Active Pharmaceutical Ingredient(s) (API)	Nevirapine (anhydrous)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitor (J05A G01)
Therapeutic indication	[HA567 trade name] is indicated for the prophylaxis against human immunodeficiency virus type 1 infection in infants of HIV-infected mothers.

1. Introduction

[HA567 trade name] is indicated for the prophylaxis against human immunodeficiency virus type 1 (HIV-1) infection in infants of HIV-infected mothers. [HA567 trade name] should not be used in patients with 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 a physician experienced in treating 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)

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 forms: the anhydrous form and the hemihydrate. Anhydrous nevirapine is used in the manufacture of [HA567 trade name]. Anhydrous nevirapine is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO Prequalification Programme.

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

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), water content, residue on ignition, heavy metals, specified and unspecified impurities (HPLC), assay (HPLC), residual solvents, bulk density and particle size distribution.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate. None of the excipients are from human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA567 trade name] are white to off-white, oval, uncoated tablet, debossed with '20' on one side and scored on other side. The necessary tests for subdivision of tablets have been conducted during development. The tablets are packaged in PVC/PVDC-aluminium blister cards and HDPE bottles with child-resistant caps.

The development of the final composition of the tablets has been described. The objective was to develop a stable product, bioequivalent to the comparator product Viramune® 200 mg tablets. The excipients selected for the core tablets are commonly used in tablets, qualitatively similar to that of the comparator product and supported by compatibility studies. The comparator product was characterised for its physical and chemical properties to define a quality target product profile. The wet granulation process was selected for manufacture of the tablets. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Four strengths, proportionally similar in composition, were developed: 200 mg, 100 mg, 50 mg and 20 mg.

Specifications

The proposed FPP specifications are pharmacopoeial based and include tests for description, identification (IR and HPLC), average weight, uniformity of weight, disintegration time, tablet breaking force, dissolution, uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), microbial limits and residual solvents.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The tablets proved to be quite stable in all the packaging configurations at the storage conditions studied. 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 2010-2011 according to internationally accepted guidelines:

A randomised, open-label, balanced, two-treatment, single-period, single-dose, parallel, bioequivalence study of Nevirapine Tablets 200 mg of Micro Labs Ltd., India with Viramune® (nevirapine) 200 mg tablets of Boehringer Ingelheim Pharmaceuticals, Inc., USA, in normal, healthy, adult, human subjects under fasting condition (study no. ARL-10-530).

The objective of the study was to compare the bioavailability of the stated Nevirapine 200 mg Tablets manufactured by Micro Labs Ltd. India (test drug) with the same dose of the reference formulation Viramune® 200 mg tablet (Boehringer Ingelheim Pharmaceuticals Inc.) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, parallel bioequivalence study in healthy subjects under fasting conditions. Each subject was assigned to receive one of the following two treatments:

Treatment T: Test – Nevirapine 200 mg Tablets (nevirapine 200 mg) Batch no. NVAG002.
Treatment R: Reference – Viramune® 200 mg tablet (nevirapine 200 mg) Batch no. 858448A.

Serial blood samples (1 pre-dose sample and 26 samples within 72 hours of the dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for nevirapine were analysed using a validated LC/MS-MS method. The limit of quantification was stated to be about 50 ng/ml for nevirapine.

The study was performed with 52 participants; data generated from a total of 50 subjects were used 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	7.5 ± 8.4	4.5 ± 4.7	-	-
C_{max} (ng/ml)	2475 ± 709 (2378)	2360 ± 477 (2310)	102.9	91.0–116.4
$AUC_{0\text{-}72hour}$ (ng·hour/ml)	115 124 ± 25 583 (112 425)	102 696 ± 19 402 (100 993)	111.3	100.9–122.8

*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 nevirapine. Accordingly, the test Nevirapine 200 mg Tablets meets the criteria for bioequivalence with regard to rate and extent of absorption

and is therefore bioequivalent to the reference Viramune® 200 mg tablet (Boehringer Ingelheim Pharmaceuticals Inc).

A biowaiver was granted for the additional tablet strengths Nevirapine 20, 50 and 100 mg (Micro Labs. Ltd, India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Nevirapine 20, 50 and 100 mg tablet strengths were determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be similar

4. Summary of product safety and efficacy

[HA567 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, [HA567 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Viramune® (Boehringer Ingelheim Pharmaceuticals Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA567 trade name] is considered acceptable when guidance and restrictions 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 [HA567 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA567 trade name] has been shown to be bioequivalent with Viramune® (Boehringer Ingelheim Pharmaceuticals Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA567 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 [HA567 trade name] was acceptable for the following indication: ' for the prophylaxis against human immunodeficiency virus type 1 infection in infants of HIV-infected mothers', and would allow inclusion of [HA567 trade name], manufactured at Micro Labs Limited, Plot No: S-155 to S-159 & N1, Phase III & IV, Verna Industrial Estate, Verna, Salcette, Goa – 403722, India, in the list of prequalified medicinal products.