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	[HA510 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited Unit II, A-42, MIDC, Patalganga, Dist: Raigad 410220, Maharashtra India Cipla Limited Unit I, A-33 & A-37/2/2, MIDC Patalganga, District: Raigad 410220, Maharashtra 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	[HA510 trade name] is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in children weighing 3-24.9kg.

1. Introduction

[HA510 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in children weighing 3–24.9kg.

[HA510 trade name] should be initiated by a healthcare 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)

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 the dispersible tablets. Anhydrous nevirapine is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the Prequalification Programme.

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

Anhydrous nevirapine is adequately controlled by its pharmacopoeial based specifications which include tests for description, solubility, identification (IR and HPLC), water content, residue on ignition, heavy metals, organic impurities (HPLC), assay (HPLC), polymorphic form (XRPD), particle size distribution, residual solvents and tapped density.

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 microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, corn starch, strawberry cream flavour (containing natural flavouring substance, maltodextrin, propylene glycol and modified starch), aspartame and magnesium stearate. None of the excipients are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a white to off-white coloured, circular shaped, biconvex uncoated dispersible tablet with central break line on one side and 'L' debossed on other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in a HDPE bottle with screw cap, containing a 1 g silica gel bag as desiccant and rayon sani coil as filler, and in PVC/PE/PVDC-Al blisters.

The development strategy was to obtain a dispersible tablet that would be bioequivalent to the comparator product, Viramune® oral suspension, containing nevirapine (as hemihydrate) 50 mg/5 ml. The excipients used in the formulation design were selected from prior knowledge and variability with respect to physicochemical and functional properties, supported by API-excipient compatibility studies. To improve the taste and flavour for the paediatric population, aspartame and strawberry cream flavour were used as sweetening and flavouring agents, respectively. The wet granulation process was chosen for the product as it would improve wettability of the poorly soluble API thus ensuring improved dissolution rate. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality and include tests for description, identification of the API (HPLC and UV), average weight, friability, hardness, disintegration (≤ 3 minutes), fineness of dispersion, water content, uniformity of dosage units (by content uniformity), dissolution (UV detection), assay (HPLC), degradation products (HPLC) and microbial examination of non-sterile products. Batch analysis data confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for 6 months at accelerated conditions. The product proved to be quite stable at both long term and accelerated storage conditions in the proposed packaging configurations. 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 according to internationally accepted guidelines.

Bioequivalence study comparing Nevimune Junior (Cipla Ltd, India) with Viramune® oral suspension (containing nevirapine 50 mg/5 ml as nevirapine hemihydrate) of Boehringer Ingelheim, Inc., USA both administered as Nevirapine 200 mg in healthy adult human subjects under fasting conditions. (study no. 09-04-302).

The objective of the study was to compare the rate and extent of absorption of the stated Nevimune Junior with the same dose of Viramune oral suspension (nevirapine 50mg/5ml). The comparison was performed as a randomized, single-dose, parallel study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – 2 tablets Nevimune Junior
(nevirapine 200 mg)
Batch no. KW8244

Treatment R: Reference – 20 ml Viramune® oral suspension (50mg/5ml)
(nevirapine 200 mg)
Batch no. 858296A

Serial blood samples (1 pre-dose sample and 23 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics $AUC_{0\text{-}72h}$, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for nevirapine in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 60 ng/ml for nevirapine.

The study was performed with 44 participants, data generated from a total of 43 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (± SD), geometric means (AUC, C_{max}) 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)	3.55 ± 4.80	3.07 ± 2.21	–	–
C_{max} (ng/mL)	2584 ± 477 (2541)	2928 ± 382 (2903)	87.5	80.4 – 95.2
$AUC_{0\text{-}72h}$ (ng·h/mL)	115483 ± 17745 (114144)	122857 ± 15983 (121822)	93.7	86.9 – 101.0

Conclusion

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 Nevimune Junior (Cipla Ltd, India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Viramune 50mg/5ml oral suspension (Boehringer Ingelheim, Inc).

A biowaiver was granted for the additional tablet strength [HA510 trade name] (Cipla Ltd, India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, [HA510 trade name] tablet strength was 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 API were determined to be similar.

4. Summary of product safety and efficacy

According to the submitted data on quality, [HA510 trade name] is a direct scale-down of Nevimune Junior. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Viramune 50mg/5ml oral suspension for which benefits have been proven in terms of clinical efficacy.

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 [HA510 trade name] is used in accordance with the Summary of Product Characteristics.

Bioequivalence

[HA510 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA510 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [HA510 trade name] was acceptable for the following indication: "**in combination with other antiretroviral medicines for the treatment of HIV-1 infection in children weighing 3-24.9kg**" and has advised that the quality, efficacy and safety of [HA510 trade name] allow inclusion of Nevimune Baby, manufactured at Cipla Ltd, Unit II, A-42, MIDC, Patalganga, District: Raigad, 410220, Maharashtra, India in the list of prequalified medicinal products.