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:	[HA537 trade name] *
Manufacturer of Prequalified Product:	Micro Labs Limited Plot No: S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa- 403722 India Tel : +91-832- 6686262 Fax : +91-832- 6686203
Active Pharmaceutical Ingredients (APIs):	Zidovudine
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF01)
Therapeutic indication:	[HA537 trade name]is indicated for • the treatment of children with HIV-1 infection in combination with other antiretroviral agents. • primary prophylaxis in newborn infants for prevention of maternal-fetal HIV-1 transmission

1. Introduction

[HA537 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients.

[HA537 trade name] is also indicated for primary prophylaxis in newborn infants for prevention of maternal-fetal HIV-1 transmission.

[HA537 trade name] should not be used for patients with clinically significant hypersensitivity to zidovudine or to any of the components in the formulation. [HA537 trade name] should be prescribed by a physician experienced in the management of HIV infection.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified zidovudine (up to 300 mg oral dose) as a BCS class 1 API. Zidovudine is thus highly soluble according to the BCS.

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

Zidovudine API is described in the Ph.Int., Ph.Eur. and the USP, and is considered well established in the WHO Prequalification Programme.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification, melting range, specific optical rotation, water content, residue on ignition, heavy metals, chromatographic purity (HPLC and TLC), assay (HPLC), residual solvents, bulk and tapped density, particle size distribution, methyl methanesulfonate (GC-MS: ≤ 2.5 ppm) and methyl-4-toluenesulfonate (HPLC: ≤ 2.5 ppm).

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 packing material.

Other ingredients

Other ingredients used in the tablet core formulation include hypromellose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The film coating contains hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The tablets are white, round shaped, biconvex and film-coated, with plain surface on one side and scored on the other side. The score-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The primary packs are PVC/PVDC–aluminium blisters and white opaque HDPE bottles with polypropylene child resistant caps, with different pack sizes.

The development of the final composition of the pediatric [HA537 trade name] has been described. The pediatric product is a direct scale down in composition of the manufacturer's already prequalified Zidovudine 300mg Tablets (HA483). The poor flow properties of the API were considered not suitable for direct compression and wet granulation was selected for manufacture of the tablet cores. The critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Similar to the comparator product (Retrovir® 300mg film-coated tablets) and the higher strength of the multisource product (Zidovudine 300mg Tablets), the 60mg tablets showed very rapidly dissolving properties in the main BCS dissolution media.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API (IR, HPLC), average weight, uniformity of weight, disintegration time, water content, uniformity of dosage units (content), dissolution, assay (HPLC), related substances (HPLC), and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term conditions and at accelerated conditions in the packaging proposed for marketing of the product. The tablets proved to be chemically and physically stable under the long-term and accelerated storage conditions and no negative trends were observed. 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

This application concerns [HA537 trade name] (Micro Labs. Limited, India). No bioequivalence study has been performed. A waiver of a proportional strength has been requested using the Zidovudine 300 mg tablets (Micro Labs. Limited, India) as reference, which has been accepted based upon a biowaiver (see HA483). No comparator 60 mg tablet is marketed. Therefore, as an exceptional case, the possibility of a biowaiver for this 60 mg pediatric formulation based on the comparison with the higher 300 mg strength has been considered acceptable for zidovudine, due to is very high solubility in all pH media from 1.2 to 6.8 (10-20 mg/ml), which ensures that the doses of 60 mg can be dissolved in 3-6 mL of the gastric and duodenal fluids.
The 60 mg tablet strength was determined to be qualitatively essentially the same as the 300 mg strength, 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

[HA537 trade name] conforms to the same relevant standards of quality, efficacy and safety as those required of the innovator product. Zidovudine 60 mg Tablets fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.
The clinical safety of this product is considered 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

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

Bioequivalence

[HA537 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, [HA537 trade name] is considered effective and safe when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA537 trade name]was acceptable for the following indications: **"treatment of children with HIV-1 infection in combination with other antiretroviral agents and primary prophylaxis in newborn infants for prevention of maternal-fetal HIV-1 transmission",** and has advised that the quality, efficacy and safety of [HA537 trade name]allow inclusion of [HA537 trade name], manufactured Micro Labs Limited, Verna Industrial Estate, Verna, Goa- 403722, India, in the list of prequalified medicinal products.