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:	[HA483 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 Ingredient (API):	Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF01).
Therapeutic indication:	[HA483 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients weighing 25 kg or more. [HA483 trade name] is also indicated for the use in pregnant women for prevention of maternal-fetal HIV-1 transmission.

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

1. Introduction

[HA483 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients weighing 25 kg or more.

[HA483 trade name] is also indicated for the use in pregnant women for prevention of maternal-fetal HIV-1 transmission.

It is recommended that therapy is given only on the advice of a physician experienced in the treatment of HIV/AIDS.

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)

Zidovudine is a class 1 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*). It is thus highly soluble in aqueous medium over the pH range 1 – 6.8.

Zidovudine API is described in the Ph.Int., Ph.Eur. and the USP. It is manufactured in several steps from thymidine.

The API is adequately controlled by its specifications which are pharmacopoeial based, with additional tests for residual solvents, bulk density, particle size, methyl methanesulfonate and methyl-4-toluenesulfonate.

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

Zidovudine 300mg Tablets are white, round biconvex, film-coated tablets, plain on both sides. The primary packs are PVDC/PVC–aluminium blisters and round, white opaque HDPE bottles with induction seal and white round, polypropylene caps (pack sizes 30, 60 and 90 tablets).

The development of the final composition of [HA483 trade name] has been described. The aim was to develop tablets, essentially similar in composition and *in vitro* release properties to the innovator product Retrovir® 300 mg tablets. 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.

Comparative dissolution studies were conducted between [HA483 trade name] and Retrovir® 300mg tablets in the three BCS media according to the requirements of WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series 937, Annex 7). Based on the similarity of the dissolution profiles, a biowaiver was allowed for Zidovudine 300 mg Tablets.

Specifications

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

Stability testing

Stability studies have been performed on three batches at 30°C/65%RH (zone IVa) as long-term conditions and at accelerated conditions. The tablets proved to be chemically and physically stable under the long-term and accelerated storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

No bioequivalence study has been performed. As zidovudine is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Retrovir® 300 mg tablet (GlaxoSmithKline, USA) and the test tablet [HA483 trade name] (Micro Labs Limited, India) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1, 4.5 and 6.8 have been shown.

Conclusion

The test tablet [HA483 trade name] (Micro Labs Limited, India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the reference Retrovir® 300 mg tablet (GlaxoSmithKline, USA).

4. Summary of product safety and efficacy

[HA483 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [HA483 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

According to the submitted data on quality and bioavailability [HA483 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Retrovir® 300 mg tablets (GlaxoSmithKline, USA) for which benefits have been proven in terms of virological and immunological efficacy.

The clinical safety of [HA483 trade name] is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. 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 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 [HA483 trade name] is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

[HA483 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, it is concluded that bioequivalence has been shown between [HA483 trade name] and Retrovir® (GlaxoSmithKline, U.S.A).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA483 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [HA483 trade name] was acceptable for the following indications: **"treatment of HIV-1 infection in combination with other antiretroviral agents in patients weighing 25 kg or more"** and **"use in pregnant women for prevention of maternal-fetal HIV-1 transmission"**, and has advised that the quality, efficacy and safety of [HA483 trade name] are acceptable to allow inclusion of [HA483 trade name], manufactured at Micro Labs Limited, Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa 403722, India, in the list of prequalified medicinal products.