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:	[HA486 trade name][*]
Manufacturer of Prequalified Product:	Hetero Labs Limited 7-2-A2 Hetero Corporate Industrial Estates Sanath Nagar Hyderabad 500 018 India
Active Pharmaceutical Ingredients (APIs):	Zidovudine
International Nonproprietary Name:	Zidovudine
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF01)
Therapeutic indication:	[HA486 trade name] is indicated for: • treatment of children with HIV-1 infection in combination with other antiretroviral agents • primary prophylaxis of HIV-1 infection in neonates

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

1. Introduction

[HA486 trade name] is indicated for the treating children with HIV-1 infection in combination with other antiretroviral agents and for primary prophylaxis of HIV-1 infection in neonates. [HA486 trade name] should not be used for patients with clinically significant hypersensitivity to zidovudine or to any of the components in the formulation. It is recommended that therapy is given only on the advice of 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)

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, and is considered well-established in the Prequalification Programme.

The API specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR), appearance of solution, specific optical rotation, loss on drying, sulphated ash, heavy metals, chromatographic purity (HPLC and TLC), assay (HPLC), residual solvents (GC), particle-size distribution and microbiological examination.

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 used in the oral solution include citric acid anhydrous, glycerol, purified water, sodium benzoate, strawberry flavour and sucrose.

Finished pharmaceutical product (FPP)

[HA486 trade name] is a colourless to pale-yellow, strawberry-flavoured liquid, presented in an opaque HDPE bottle with child-resistant cap. The bottle is packed in an outer carton containing also a 10-ml and a 1.5-ml polypropylene oral dosing syringe.

Pharmaceutical development and manufacture

The development of the final composition of [HA486 trade name] has been described. The excipients selected are also present in the comparator product, Retrovir® 100 mg/10 ml oral solution. The antimicrobial preservative content was based on analysis of the comparator product and on antimicrobial efficiency studies. The pH of the multisource product was selected on grounds of the limits set for Zidovudine oral solution in the Ph.Int and USP, as well as analysis of the comparator product. The container closure system was found appropriate for the product.

The manufacturing process for the oral solution is well described and consists of conventional preparation of the solution, adjustment of pH, filtration and bottle filling. The critical steps were identified and appropriate in-process controls set. Validation data presented for three batches demonstrated the consistency of the process and the quality of the product.

Specifications

The finished product specifications include appropriate tests for description, identification of the APIs (TLC, HPLC) and of sodium benzoate, mass uniformity of delivered doses, pH, related substances (HPLC), assay (HPLC), preservative content (HPLC) and microbial examination. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been performed on the same three batches used in the process validation at 25°C/60%RH as long-term storage conditions and at accelerated conditions. The data showed a slow increase in related substances, including thymine, though all attributes were within the agreed specifications at both storage conditions. The data provided support the proposed shelf life and storage conditions as defined in the SmPC.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

No bioequivalence study has been performed on [HA486 trade name] (Hetero Labs Limited, India), a solution for oral administration. A waiver has been requested with Retrovir® (zidovudine) 10 mg/ml oral solution as comparator. It has been adequately substantiated that the formulation contains the same concentration of API as the comparator, is essentially similar to the comparator product, and evidence is provided to demonstrate that excipients have no effect on the absorption of the API.

Accordingly, as the [HA486 trade name] (Hetero Labs Limited, India) is a solution for oral administration, it is therefore considered bioequivalent to the Retrovir® (zidovudine) 10 mg/ml oral solution (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA486 trade name] conforms 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, Retrovir® 100 mg/10 ml oral solution.

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

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

Bioequivalence

Comparability between the reference Retrovir® 100 mg/10 ml oral solution (GlaxoSmithKline) and the test product [HA486 trade name] (Hetero Labs Limited, India) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA486 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, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit–risk profile of [HA486 trade name] was acceptable for the following indications: treatment of children with HIV-1 infection in combination with other antiretroviral agents and primary prophylaxis of HIV-1 infection in neonates, and has advised inclusion of [HA486 trade name], manufactured at Hetero Labs Limited, Hyderabad, India, in the list of prequalified medicinal products.