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:	[HA526 trade name] *
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block : N2, Village Theda P. O. Lodhi Majra Tehsil Nalagarh, District Solan Himachal Pradesh India Tel: +91-01795 661400 Fax: +91-01795 661452
Active Pharmaceutical Ingredients (APIs):	Zidovudine
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF01)
Therapeutic indication:	[HA526 trade name] is indicated for - the 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

[HA526 trade name] is indicated for the treatment of children with HIV-1 infection in combination with other antiretroviral agents and for primary prophylaxis of HIV-1 infection in neonates.

[HA526 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)

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.

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

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

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, glycerin, sodium benzoate, strawberry flavour, sucrose and purified water. None of the other ingredients are derived from animal or human source.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Zidovudine 50mg/5ml Oral Solution is a clear, colourless to pale yellow syrupy flavoured liquid, presented in a white, round HDPE bottle with child resistant polypropylene closure with EPE wad. The dosing devices provided for low doses and higher doses are a 3ml syringe and a 10 ml syringe, respectively, which are used with an adaptor. The measuring devices were demonstrated to deliver doses accurately in the dosing range.

The manufacturer has provided data to demonstrate that zidovudine is adequately soluble for formulation of the oral solution. The objective of the developmental activities was to obtain a stable and robust formulation of zidovudine oral solution, comparable to the innovator product, Retrovir® 100 mg/10 ml oral solution, with respect to strength, flavour, composition and physicochemical and microbial properties. Based on the data from the innovator and USP monograph the pH range of zidovudine oral solution was set, sodium benzoate was selected as the preservative and citric acid as the buffer system. 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, making up to volume, filtration and bottle filling. The critical steps were identified and appropriate in-process controls set.

Specifications

The finished product specifications are pharmacopoeial based and include appropriate tests for description, identification of the API (HPLC and TLC) and of sodium benzoate (HPLC), weight per ml, deliverable volume, pH, related substances (HPLC), assay (HPLC), antimicrobial preservative content (HPLC) and microbial quality. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies were conducted at 30ºC/75%RH as long-term storage conditions and for six months at accelerated conditions. The data showed a slow increase in related substances, 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. Data were also provided in support of the in-use storage period after first opening of the bottle as stated in the SmPC.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

A biowaiver was granted for the Zidovudine 10 mg/mL oral solution manufactured by Macleods Pharmaceuticals Ltd., India, in accordance to the WHO guideline. In comparison with the innovator Retrovir 10 mg/mL oral solution (GSK), the test product was determined to be qualitatively essentially the same and quantitatively comparable with regard to the used excipients. The differences are considered not to affect the absorption of zidovudine.

4. Summary of Product Safety and Efficacy

[HA526 trade name] conforms to the same appropriate standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality Zidovudine 50 mg/5 mL oral solution is pharmaceutically and therapeutically equivalent and thus interchangeable the innovator product Retrovir® 10 mg/mL oral solution for which benefits have been proven in terms of clinical efficacy.

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 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 Zidovudine 50 mg/5 mL Oral Solution is used in accordance with the SmPC.

Bioequivalence

[HA526 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence [HA526 trade name] and Retrovir 10 mg/mL oral solution (GSK) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA526 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 the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit-risk profile of [HA526 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 that the quality, efficacy and safety of [HA526 trade name] allow inclusion of Zidovudine 50 mg/5 ml Oral Solution, manufactured at Macleods Pharmaceuticals Limited, Tehsil Nalagarh, District Solan,Himachal Pradesh, India in the list of prequalified medicinal products.