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	[HA523 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block: N2, Village Theda P. O. Lodhi Majra Tehsil Baddi , Dist. Solan Himachal Pradesh, India Tel: +91-01795 661400 Fax: +91-01795 661452
Active Pharmaceutical Ingredient(s) (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside reverse transcriptase inhibitors (J05AF05).
Therapeutic indication	[HA523 trade name] is indicated for the treatment of HIV-1 infection in infants and children weighing 2 kg to less than 14 kg in combination with other antiretroviral agents.

1. Introduction

[HA523 trade name] is indicated for the treatment of HIV-1 infection in infants and children weighing 2 kg to less than 14 kg in combination with other antiretroviral agents.

[HA523 trade name] should be prescribed by a physician 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)

Based on scientific principles the WHO Prequalification of Medicines Programme has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus highly soluble in aqueous medium over the pH range 1 – 6.8.

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

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification, light absorption, specific optical rotation, melting range, water content, residue on

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

ignition, heavy metals, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), chromatographic purity (HPLC), assay (HPLC), residual solvents, particle size and bulk density (untapped).

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 oral solution include banana flavour, citric acid anhydrous, methyl paraben, propyl paraben, propylene glycol, sodium hydroxide, purified water, sodium citrate dihydrate, strawberry flavour and sucrose. None of the excipients have been derived from animal or human source.

Finished pharmaceutical product (FPP)

The oral solution is a clear, colourless to pale yellow, flavoured liquid, presented in a white, round HDPE bottle with child resistant closure with EPE wad. Each bottle contains 240 mL oral solution. A 10 mL oral dosing syringe, duly calibrated, is provided for accurate dosage measurement.

Pharmaceutical development and manufacture

The objective was to develop a stable and robust formulation of lamivudine oral solution (10 mg/mL) comparable to the comparator product (Epivir® 10mg/mL oral solution). As part of the predevelopment studies the comparator product has been characterized for its chemical and physical characteristics. The excipients selected are qualitatively the same as present in the comparator product, with the sweetener, sucrose, quantitatively the same. Prototype formulation batches were designed to optimize the pH, buffer concentration, preservative content, and process parameters. The oral solution contains methyl- and propyl hydroxybenzoate as preservatives, which were shown to be effective to control the growth of microorganisms throughout the shelf life and during the in-use period.

The manufacturing process consists of conventional preparation of the solution, adjustment of pH and volume, filtration and bottle filling. The critical steps were identified, and appropriate in-process controls set. Validation data 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 API and preservatives, weight per mL, deliverable volume, pH, related substances (HPLC), residual solvents, assay (HPLC), antimicrobial preservative content (HPLC) and microbial quality. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for 6 months at accelerated conditions in the packaging proposed for marketing of the product. The data showed that the product is quite stable at both storage conditions, with a slight increase in degradation products with time and a slight decrease in preservative content. The data support the proposed shelf life and storage conditions as defined in the SmPC. In-use stability studies indicated that the product can be used for 30 days after first opening of the bottle.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

A biowaiver was granted for the [HA523 trade name] manufactured by Macleods Pharmaceuticals Ltd., India, in accordance to the WHO guideline. In comparison with the innovator Epivir® 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 lamivudine.

4. Summary of product safety and efficacy

[HA523 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [HA523 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [HA523 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA523 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [HA523 trade name] and Epivir® 10 mg/mL oral solution (GlaxoSmithKline) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA523 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA523 trade name] was acceptable for the following indication: ' **for the treatment of HIV-1 infection in infants and children weighing 2 kg to less than 14 kg in combination with other antiretroviral agents**', and would allow inclusion of [HA523 trade name], manufactured at Macleods Pharmaceuticals Limited, Block N2, Village Theda, P. O. Lodhi Majra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, India in the list of prequalified medicinal products.