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	[TB323 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited Plot No. 15/ A 2nd Phase Kumbalgodu Industrial Area 560074 Bangalore Karnataka India
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinones antibacterials (J01XX08)
Therapeutic indication	[TB323 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB323 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in adults and adolescents weighing at least 45 kg.

[TB323 trade name] is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

[TB323 trade name] should be initiated by a health care provider experienced in the management of tuberculosis 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 Team – Medicines (PQTm) has identified linezolid (up to 600 mg oral dose) as a BCS class I API, eligible for BCS-based biowaiver application. The API is thus BCS highly soluble.

The APIMF of linezolid has been accepted through WHO's APIMF procedure. Details pertaining to manufacturing process development of Linezolid API have been provided in the restricted part of the API master file. Linezolid manufactured by the API manufacturer is the S-isomer. Linezolid exhibits polymorphism; the API manufacturer consistently produces form-II which is stable.

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

The API specifications include tests for description, solubility, identification (IR, HPLC and XRPD), loss on drying, specific optical rotation, sulphated ash, heavy metals, assay (HPLC), related substances (HPLC), R-Isomer content (HPLC), residual solvents (GC), synthetic impurities (GC, HPLC) and particle size distribution. Synthesis related genotoxic impurities are controlled at justified levels.

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 core tablet formulation include maize starch, sodium starch glycolate, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide and macrogol/polyethylene glycol. None of the excipients are derived from human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, capsule-shaped, biconvex, film-coated tablet, with a break line on one surface and plain on the other surface. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in Alu/Alu strip packs.

The development of the multisource product was based on the pharmacokinetic and physico-chemical properties known for the WHO recommended comparator product, Zyvox® 600 mg film-coated tablets, which is an immediate-release solid dosage form for oral administration. The excipients selected are generally excipients used in tablet formulations. The excipients remain qualitatively same as that of the comparator product.

Due to the poor flow properties of the API, wet granulation method was selected as the manufacturing process.

Specifications

The finished product specifications include tests for appearance, identification of the API (HPLC, UV), average mass, disintegration time, tablet dimensions, uniformity of dosage units (by mass variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), microbial limit test and residual solvents (GC). The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30^{o}C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no negative trend observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the summary of product characteristics (SmPC) are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

No bioequivalence study has been performed. As linezolid 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 Zyvox® 600 mg tablet (Pharmacia Limited) and the test [TB323 trade name] (Micro Labs. Ltd., India) regarding the qualitative and quantitative composition of the

formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 have been shown. Accordingly, the test tablet [TB323 trade name] (Micro Labs. Ltd., India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the WHO-recommended comparator, Zyvox® 600 mg tablet (Pharmacia Limited).

4. Summary of product safety and efficacy

[TB323 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO-recommended comparator product. [TB323 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the SmPC are taken into account. 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 [TB323 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB323 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB323 trade name] and Zyvox® 600 mg tablet (Pharmacia Limited) are bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB323 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 [TB323 trade name] was acceptable for the following indication: '**in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*'**, and would allow inclusion of [TB323 trade name], manufactured at Micro Labs Limited, Plot No. 15/A 2nd Phase, Kumbalgodu Industrial Area, *Bengaluru* 560 074, Karnataka, India, in the list of prequalified medicinal products.