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	[TB389 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited [Unit 3] 92 Sipcot Industrial Complex Hosur-635126 Tamil Nadu India.
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinones antibacterials, (J01XX08)
Therapeutic indication	[TB389 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB389 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis.*

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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)

Linezolid has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that these APIs, used in the manufacture of [TB389 trade name], are of good quality and manufactured in accordance with WHO good manufacturing practices.

API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, ethyl cellulose, sucralose, peppermint flavour, orange flavour, crospovidone, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. The excipients are supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, circular flat-faced, beveled edge, uncoated tablet with deep break-line on one face and shallow convex debossed with "LD" on other face. 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 strips.

The aim of the development work was to formulate dispersible tablets containing linezolid which is bioequivalent to the WHO recommended comparator product, Zyvoxid® 600 mg film-coated tablets, which is an immediate release solid dosage form for oral administration. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The selection of excipients was based on previous formulation experience and knowledge about excipients that have been used successfully in approved dispersible tablets by the manufacturer. The taste was masked by coating the API particles with ethyl cellulose (used as a dispersion containing pore forming agents to enhance release of the API in the stomach). Sweeteners and flavouring agents were also included to mask the unpleasant taste of the API. Due to the very poor flow properties of linezolid API, a top spray granulation method was selected as the manufacturing process for the dispersible tablets in view of its conventional acceptability and robustness. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for appearance, identification of the API (HPLC and PDA detector), average mass, tablet dimensions, disintegration time, resistance to crushing, friability, fineness of dispersion, subdivision of tablets, water content (KF), uniformity of dosage units (by mass variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC) and microbial limit test. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The tablets showed an increasing trend although within limits with respect to water content. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021 according to internationally accepted guidelines.

An open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover, single-dose, oral bioequivalence study of Linezolid dispersible tablets 150 mg (4 × 150 mg), manufactured by Micro Labs Limited, India and Zyvoxid® 600 mg filmomhulde tabletten (linezolid), of Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel in healthy, adult, human subjects under fasting conditions (study no. 054-20).

The objective of the study was to compare the bioavailability of the stated Linezolid 150 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Zyvoxid® 600 mg tablet (Pfizer) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 4 dispersible tables Linezolid 150 mg (linezolid 600 mg) Batch no. LLAH002A.
Treatment R: Reference – Zyvoxid® 600 mg tablet (linezolid 600 mg) Batch no. AT6650.

The dispersible tablets were dispersed in 50 ml water and administered. The reference was administered with 240 mL water. A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for linezolid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for linezolid.

The study was performed with 36 participants; data generated from a total of 36 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for linezolid as well as statistical results are summarised in the following table:

Linezolid

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.17 ± 0.85	1.08 ± 0.88	–	–
C_{max} (µg/mL)	16.7 ± 3.8 (16.3)	17.4 ± 3.9 (17.0)	95.8	89.3 – 102.8
AUC_{0-t} (µg h/mL)	134 ± 28 (131)	127 ± 24 (124)	105.4	101.9 – 109.1
AUC_{0-inf} (µg.h/mL)	134 ± 28	127 ± 24	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding linezolid. Accordingly, the test Linezolid 150 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Zyvoxid® 600 mg tablet (Pfizer).

4. Summary of product safety and efficacy

[TB389 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [TB389 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvoxid® 600 mg tablet (Pfizer) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB389 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer 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 [TB389 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB389 trade name] has been shown to be bioequivalent with Zyvoxid® 600 mg tablet (Pfizer).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB389 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 [TB389 trade name] was acceptable for the following indication: '**in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis***', and would allow inclusion of [TB389 trade name], manufactured at Micro Labs Limited [Unit 3], 92 Sipcot Industrial Complex, Hosur-635126, Tamil Nadu, India in the list of prequalified medicinal products.