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	[TB409 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited EPIP, SIDCO Industrial Complex Kartholi, Bari Brahmana Jammu (J& K) – 181133 India
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Other antibacterials, (J01XX08)
Therapeutic indication	[TB409 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB409 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 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)

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 applications. The API is thus regarded BCS highly soluble.

The APIMF of linezolid has been accepted through WHO's APIMF procedure. Details pertaining to manufacturing process development of linezolid API has 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.

The API specifications include tests for description, solubility, identification (IR, HPLC and p-XRD), water determination, residue on ignition, heavy metals, organic impurities (HPLC), genotoxic impurities (HPLC and GC), assay (HPLC), enantiomeric purity (HPLC), residual solvents (GC) and particle size distribution. Synthesis related genotoxic impurities are controlled at justified levels.

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

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, microcrystalline cellulose, colloidal silicon dioxide, raspberry flavour, sodium starch glycolate, ethyl cellulose, hypermellose, mannitol, crospovidone, aspartame, peppermint flavour and magnesium stearate, all being controlled by acceptable specifications. The raspberry flavour contains flavouring substances, maltodextrin, gum arabic, propylene glycol and sodium benzoate whilst the peppermint flavour contains an emulsifier, maltodextrin and flavouring substances. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablets have a break line on one side and are plain on other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in aluminium foil strips and amber plastic (PVC/PVDC) on aluminium foil blister packs.

The objective of the formulation development was to develop a robust, stable and prototype formula of linezolid dispersible tablet that is bioequivalent to the WHO recommended comparator product, Zyvox® (linezolid) 600 mg film-coated tablets. The excipients were selected based on the properties of the API, literature search and API-excipient compatibility studies. Sweetener and flavouring agents were used to make the dispersible tablets more palatable. To achieve satisfactory flow properties and compressibility of the API, a hydro-alcoholic wet granulation was selected for the manufacturing process. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk assessment by the applicant, the potential presence of nitosamine impurities was declared, however confirmatory test results for the FPP did not find detectable levels of the suspected nitrosamines.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), fineness of dispersion, disintegration time, water content (KF), average weight, assay (HPLC), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), degradation products (HPLC), residual solvents (GC), subdivision of tablets and microbial limits. The analytical methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage 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 SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2023 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study comparing [TB409 trade name] (1 x 4 tablets) manufactured by Lupin Limited, India with Zyvoxid® 600 mg (linezolid) film-coated tablets of Pfizer ApS, 2750 Ballerup, Danmark in healthy, adult, human subjects under fasting conditions (study no. LBC-23-044).

The objective of the study was to compare the bioavailability of the stated [TB409 trade name] manufactured by/for Lupin Limited, India (test drug) with the reference formulation Zyvoxid® 600 mg tablet (Pfizer ApS) 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 tablets [TB409 trade name] (linezolid 600 mg) Batch no. J390308
Treatment R:	Reference – 1 tablet Zyvoxid® 600 mg (linezolid 600 mg) Batch no. FK3807

The test dispersible tablets were dispersed in 30 mL water (+ 20 mL of rinsing water) and administered. The reference was administered with 240 mL water. A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 24 participants; data generated from a total of 24 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)	1.59 ± 0.98	1.56 ± 0.98	–	–
C_{max} (µg/mL)	13.7 ± 2.3 (13.5)	14.1 ± 2.7 (13.8)	97.4	91.9 – 103.3
AUC_{0-t} (µg·h/mL)	120 ± 25 (118)	123 ± 24 (121)	97.8	93.0 – 102.8
AUC_{0-inf} (µg·h/mL)	123 ± 26 (120)	125 ± 26 (123)	97.9	93.0 – 103.0

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and Cmax 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 ApS).

4. Summary of product safety and efficacy

[TB409 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, [TB409 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvoxid® 600 mg tablet (Pfizer ApS) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB409 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 [TB409 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB409 trade name] has been shown to be bioequivalent with Zyvoxid® 600 mg tablet (Pfizer ApS).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB409 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 [TB409 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 [TB409 trade name], manufactured at Lupin Limited, EPIP, SIDCO Industrial Complex, Kartholi, Bari Brahmana, Jammu (J& K) – 181133, India in the list of prequalified medicinal products.