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	[TB365 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Ltd Plot No. 11,12 & 13 Indore Special Economic Zone Pharma Zone Phase II, Sector III Pithampur, District Dhar Madya Pradesh, 454 775 India.
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinones antibacterials (J01XX08)
Therapeutic indication	[TB365 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 45kg. [TB365 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.

1. Introduction

[TB365 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.

[TB365 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.

[TB365 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 applications. The API is thus BCS highly soluble.

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

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.

The API specifications include tests for description, solubility, identification (IR, HPLC and PXRD), residue on ignition, water determination, assay (HPLC), related substances (HPLC, LCMS/MS and GC), enantiomeric purity (HPLC), residual solvents (GC) 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, colloidal anhydrous silica and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, hydroxypropyl cellulose, titanium dioxide, macrogol/polyethylene glycol and talc. Magnesium stearate is of vegetable origin. TSE/BSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, film-coated, oval-shaped, biconvex, bevelled edge tablet, debossed with **LN600** on one side and **M** on the other side of the tablet which also has a score line. The surface of the tablet may have a granular appearance.

The score-line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in round, white, opaque HDPE bottles and closed with white opaque polypropylene screw caps with aluminium induction sealing liner wad. Each bottle also contains a 1g silica gel/activated carbon canister.

The objective of the formulation development was to develop a product which is pharmaceutically acceptable, stable and bioequivalent to the WHO recommended comparator product, Zyvoxid® 600 mg film-coated tablets. The selection of excipients was based on the qualitative composition of the comparator product, supported by API-excipient compatibility studies. Due to the very poor flow properties of the API and high dose of the API in the formulation, wet granulation was selected as the manufacturing process. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (HPLC, UV) and colour identification test for titanium dioxide, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by mass variation), 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 conditions in the package 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 2018 according to internationally accepted guidelines.

A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Linezolid tablets 600 mg manufactured by Mylan Laboratories Limited, India with Zyvoxid® (linezolid) tablets 600 mg of Pfizer in normal healthy, male, adult, human subjects under fasting conditions (study no. C17280).

The objective of the study was to compare the bioavailability of the stated Linezolid tablets 600 mg manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Zyvoxid® (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 – 1 tablet Linezolid tablets 600 mg (linezolid 600 mg) Batch no. 2014313.
Treatment R:	Reference – 1 tablet Zyvoxid® (linezolid 600 mg) Batch no. N39478.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 36 hours 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 150 ng/mL for linezolid.

The study was performed with 28 participants; data generated from a total of 28 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)	1.54 ± 0.92	1.11 ± 0.81	–	–
C_{max} (µg/mL)	16.0 ± 4.3 (15.5)	17.7 ± 4.7 (17.1)	90.5	82.5 – 99.4
AUC_{0-t} (µg ·h/mL)	96.8 ± 18.4 (95.1)	97.0 ± 18.8 (95.2)	99.9	96.5 – 103.3
AUC_{0-inf} (µg ·h/mL)	99.0 ± 19.0 (97.2)	99.3 ± 19.6 (97.4)	99.8	96.4 – 103.4

The results of the study show that pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding linezolid. Accordingly, the test Linezolid 600 mg tablet meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Zyvoxid® (Pfizer).

4. Summary of product safety and efficacy

[TB365 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, [TB365 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvoxid® (Pfizer) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB365 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 [TB365 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB365 trade name] has been shown to be bioequivalent with Zyvoxid® (Pfizer).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB365 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 [TB365 trade name] was acceptable for the following indication: "**in combination with other anti-tuberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in patients weighing at least 45 kg**", and would allow inclusion of [TB365 trade name] manufactured at Mylan Laboratories Limited, Plot No. 11,12 & 13, Indore Special Economic Zone, Pharma Zone, Phase II, Sector III, Pithampur, District Dhar, Madya Pradesh, 454 775, India, in the list of prequalified medicinal products.