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	[TB297 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block No. 2 Village Theda P.O. Lodhi Majra Tehsil Baddi, Dist.: Solan Himachal Pradesh, 174101 India
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinones antibacterials, (J01XX08)
Therapeutic indication	[TB297 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB297 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

[TB297 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB297 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.

[TB297 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.

[*] 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. Linezolid is a white to off white, crystalline powder. It contains one chiral carbon atom; the S-enantiomer is the pharmaceutical form. The manufacture of linezolid entails several chemical steps and is described in full in the restricted part of the API master file. The API shows polymorphism; form II is consistently produced.

The API specifications include tests for description, solubility, identification (IR, HPLC), specific optical rotation, loss on drying, residue on ignition, heavy metals, enantiomeric purity (chiral HPLC, R-isomer ≤ 0.10 %), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic form (XRPD), particle size (laser diffraction) and metals (Li, Ni, Co, Pd by ICPMS). 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 microcrystalline cellulose, sodium starch glycolate, povidone, hydrogenated polyoxyl castor oil, crospovidone, colloidal anhydrous silica and magnesium stearate. The film-coat contains hypromellose, purified talc, titanium dioxide and macrogol. TSE / BSE free attestations have been provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, capsule shaped, biconvex film coated tablet with deep score on both sides. The score lines are intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are presented in clear PVC-aluminium blister packs and aluminium-aluminium strip packs.

The development of the final composition of the multisource product has been described. The objective of the developmental activities was to obtain a stable and robust formulation of Linezolid 600 mg Tablets that would be bioequivalent to the WHO recommended comparator product marketed in USA, namely ZYVOX® tablets 600 mg. The selection of excipients in the formulation of the core tablets was based on their suitability to achieve the desired tablet characteristics and their demonstrated compatibility with linezolid.

A wet granulation approach was adopted for manufacturing of the core tablets. The levels of the functional excipients in the formulation were optimised to ensure acceptable physical characteristics of the tablets – like hardness, friability, uniformity of weight and disintegration time – and in particular to obtain dissolution profiles similar to those of the comparator product for biowaiver purposes. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and colorant, average weight, disintegration time, loss on drying, uniformity of dosage units (by weight variation), dissolution (UV detection), related substances (HPLC), residual solvents (GC), assay (HPLC), subdivision of tablets and microbiological examination. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions in both pack types, with only slight degradation of the API. 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 2010 according to internationally accepted guidelines.

Study title: Bioequivalence study of single dose Linezolid tablets 600 mg (each tablet contains 600 mg linezolid) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Zyvox® (linezolid) tablets 600 mg (each tablet contains 600 mg linezolid) distributed by Pharmacia & Upjohn Co., USA, in healthy, adult, human subjects under fasting condition (study no. BEQ-448-LINE-2009).

The objective of the study was to compare the bioavailability of the stated Linezolid 600 mg tablets manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Zyvox® (Pharmacia & Upjohn Co.) 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 treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Linezolid 600 mg (linezolid 600 mg) Batch no. BLN001
Treatment R:	Reference – 1 tablet Zyvox® (linezolid 600 mg) Batch no. C090125

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 48 h 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 100 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)	1.30 ± 0.80	1.63 ± 0.78	-	-
C_{max} (µg /mL)	14.0 ± 2.8 (13.8)	12.9 ± 1.9 (12.8)	107.6	101.9 – 113.6
AUC_{0-t} (µg·h/mL)	102 ± 20 (100)	107 ± 25 (104)	96.2	91.9 – 100.7
AUC_{0-inf} (µg·h/mL)	106 ± 23 (104)	112 ± 29 (109)	95.9	91.5 – 100.6

Conclusion

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 600 mg Tablets meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the comparator Zyvox® (Pharmacia & Upjohn Co.).

4. Summary of product safety and efficacy

[TB297 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, [TB297 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvox® (Pharmacia & Upjohn Co.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB297 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 [TB297 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB297 trade name] has been shown to be bioequivalent with Zyvox® (Pharmacia & Upjohn Co.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB297 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 [TB297 trade name] was acceptable for the following indication: '**in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and adolescents weighing at least 30kg**', and would allow inclusion of [TB297 trade name], manufactured at Macleods Pharmaceuticals Limited, Block No.: N2, Village Theda, P.O. Lodhi Majra, Tehsil Baddi, Dist.: Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.