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	[TB350 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)	Oxazolidinone antibacterials, (J01XX08)
Therapeutic indication	[TB350 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in patients weighing at least 45 kg. It may also be used in patients with lower weights who weigh at least 5 kg, in the absence of a more suitable formulation. [TB350 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

[TB350 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in patients weighing at least 45 kg.

It may also be used in patients with lower weights who weigh at least 5 kg, in the absence of a more suitable formulation.

[TB350 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.

[TB350 trade name] should be initiated by a health care provider experienced in the management of tuberculosis.

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

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 600mg oral dose) as a BCS class I API, eligible for BCS-based biowaiver applications. 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 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), water determination, residue on ignition, heavy metals, related substances (HPLC with UV and MS detection, and GC), assay (HPLC), 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 lactose monohydrate, polacrilin potassium, hypromellose, colloidal silicon dioxide and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide. 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 coloured, oval shaped, bevelled edges, biconvex, film coated tablet having score-line on one side and plain on other side.

The score-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by the FPP specifications. The tablets are packaged in PVC/PVDC-Alu blister and PVC-Alu blister packs.

The objective of the formulation development was to develop a product which is bioequivalent to the WHO recommended comparator product, Zyvox® 600 mg film-coated tablets. The formulation development was based on the evaluation of API properties, characterization of the comparator product and API-excipient compatibility studies. To improve the flow properties and compressibility of the API, wet granulation was selected as the manufacturing process.

Specifications

The finished product specifications include tests for description, identification (HPLC, UV) and colour identification test for titanium dioxide, average weight, uniformity of dosage units (by mass variation), water content, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), tablet divisibility (by mass) 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 packages 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 2016 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of [TB350 trade name] of Lupin Limited, India with Zyvox® (linezolid) tablets 600 mg of Pfizer Pharmacia & Upjohn Co, in normal, healthy, adult, male human subjects under fasting conditions (study no. ARL/16/111).

The objective of the study was to compare the bioavailability of the stated linezolid 600 mg tablets manufactured by/for Lupin Limited, India (test drug) with the reference formulation Zyvox® (Pfizer 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 two treatments in a randomized fashion:

Treatment T: Test – 1 tablet [TB350 trade name] (linezolid 600 mg) Batch no. J690085.
Treatment R: Reference – 1 tablet Zyvox® (linezolid 600 mg) Batch no. J07108.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 24h 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 27 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)	1.71 ± 1.02	1.69 ± 1.18	–	–
C_{max} (µg /mL)	13.6 ± 2.1 (13.5)	14.3 ± 2.0 (14.2)	94.7	91.3 – 98.3
AUC_{0-t} (µg·h/mL)	111 ± 30 (108)	118 ± 25 (115)	94.0	89.4 – 98.8
AUC_{0-inf} (µg·h/mL)	118 ± 40 --	124 ± 30 --	-	-

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 [TB350 trade name] meets the criteria for

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

4. Summary of product safety and efficacy

[TB350 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 [TB350 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvox® for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB350 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 [TB350 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB350 trade name] has shown to be bioequivalent with Zyvox® (Pfizer Pharmacia & Upjohn Co.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB350 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 [TB350 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. It may also be used in patients with lower weights who weigh at least 5 kg, in the absence of a more suitable formulation. [TB350 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.”** and has advised that the quality, efficacy and safety of [TB350 trade name] allow inclusion of [TB350 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.