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

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| **Name of the Finished Pharmaceutical Product** | [TB299 trade name]* |
| **Manufacturer of Prequalified Product** | Hetero Labs Limited, Unit – V<br>Sy No. 439, 440, 441 & 458<br>TSIIC Formulation SEZ<br>Polepally village, Jadcherla<br>Mandal Mahaboob Nagar District<br>Telangana<br>India |
| **Active Pharmaceutical Ingredient(s) (API)** | Linezolid |
| **Pharmaco-therapeutic group (ATC Code)** | Oxazolidinones antibacterials, (J01XX08) |
| **Therapeutic indication** | [TB299 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis n adults and adolescents weighing ≥30 kg.*<br>[TB299 trade name] is only indicated as a second-line antimycobacterial drug when<br>use of first-line drugs is not appropriate due to resistance or intolerance |

## 1. Introduction

[TB299 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in adults and adolescents weighing ≥30 kg.

[TB299 trade name] only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

[TB299 trade name] should be prescribed by a health care provider experienced in the management of tuberculosis

## 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*.

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

## 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. Linezolid 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, and XRPD), loss on drying, residue on ignition, heavy metals, specific optical rotation, related substances and other synthesis impurities (HPLC with UV and MS detection, and GC), assay (HPLC), enantiomeric purity (chiral HPLC; ≤ 0.08%), residual solvents (GC), particle size distribution and microbiological examination. 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, maize starch, hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol and carnauba wax. TSE / BSE free attestations have been provided for the excipients.

## Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a white to off-white, oval shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side with score line and 'L' and '8' separated by a score line on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in a HDPE bottle containing a canister with silica gel desiccant and Alu-Alu blister pack.

The development of the final composition of the multisource product has been described. The objective was to develop a stable tablet, bioequivalent to the comparator product, Zyvoxid® 600 mg film-coated tablets, which is an immediate release solid dosage form for oral administration. The comparator product was investigated for various parameters, including dissolution profiles in BCS related media which served as target profiles for the multisource product. The excipients selected are in common use with their stated functions. The core tablets are manufactured via a wet granulation process. It has been demonstrated that the API retains its polymorphic form during manufacture. 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, water content (KF), dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), hardness, subdivision of tablets and microbiological examination.

*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 packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no negative trends 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 2014 according to internationally accepted guidelines.

Study title: A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Linezolid 600 mg tablets of Hetero Labs Limited, India and Zyvoxid® (linezolid) 600 mg Filmtabletten of Pharmacia GmbH/Pfizer Pharma GmbH, Berlin, in healthy human adult subjects, under fasting conditions (study no. 3412/14).

The objective of the study was to compare the bioavailability of the stated Linezolid 600 mg tablets manufactured for/by Hetero Labs Ltd., India (test drug) with the reference formulation Zyvoxid® (Pharmacia GmbH/Pfizer Pharma GmbH) and to assess bioequivalence. The comparison was performed as a single center, 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:

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| Treatment T: | Test – 1 tablet Linezolid 600 mg (linezolid 600 mg) Batch no. LIN113001. |
| Treatment R: | Reference – 1 tablet Zyvoxid® (linezolid 600 mg) Batch no. V131600 |

An8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36 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 0.125 µg/mL for linezolid.

The study was performed with 32 participants; data generated from a total of 30 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) | 1.99 ± 1.07 | 1.77 ± 1.12 | – | – |
| $C_{max}$ (µg /mL) | 13.8 ± 2.7 (13.5) | 13.9 ± 2.7 (13.7) | 98.7 | 93.6 – 104.1 |
| $AUC_{0-t}$ (µg·h/mL) | 145 ± 32 (141) | 148 ± 30 (145) | 97.5 | 93.4 – 101.7 |
| $AUC_{0-inf}$ (µg·h/mL) | 150 ± 37 (146) | 153 ± 33 (150) | 97.6 | 93.3 – 102.1 |

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 tablet Linezolid 600 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Zyvoxid® (Pharmacia GmbH/Pfizer Pharma GmbH).

## 4. Summary of product safety and efficacy

[TB299 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, [TB299 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zyvoxid® for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB299 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 Linezolid 600 mg Tablets is used in accordance with the SmPC**.**

### Bioequivalence

[TB299 trade name] has shown to be bioequivalent with Zyvoxid®, (Pharmacia GmbH/Pfizer Pharma GmbH), Germany.

### Efficacy and Safety

Regarding clinical efficacy and safety, [TB299 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 [TB299 trade name] was acceptable for the following indication: "as second-line therapy **in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in adults and adolescents weighing ≥30 kg"**, and would allow inclusion of [TB299 trade name], manufactured at Hetero Labs Limited, Unit – V, Sy No. 439, 440, 441 & 458, TSIIC Formulation SEZ, Polepally village, Jadcherla Mandal, Mahaboob Nagar District, Telangana, India in the list of prequalified medicinal products.