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	[TB391 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Plot No.50 to 54A SEZ, Phase II Pithampur, Dist: Dhar Madhya Pradesh, 454774 India
Active Pharmaceutical Ingredients (APIs)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Other antibacterials, ATC code: J01XX08
Therapeutic indication	[TB391 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB391 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 a review of availability solubility data, the WHO Prequalification Team – Medicines (PQT/MED) has identified linezolid (up to 600mg oral dose) provisionally as a BCS class I API in support of BCS-based biowaiver applications. The API can thus be regarded as BCS highly soluble. 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), loss on drying, residue on ignition, heavy metals, enantiomeric purity (chiral HPLC, R-isomer $\leq$ 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.

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

Other ingredients

Other ingredients used in the tablet formulation include hydroxypropyl cellulose, ethyl cellulose, polyethylene glycol, microcrystalline cellulose, crospovidone, mannitol, sodium chloride, sodium citrate dihydrate, aspartame, saccharin sodium, powdarome peppermint premium, powdarome strawberry premium, flavour peppermint and magnesium stearate.

The excipients are supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white coloured, capsule shaped, biconvex uncoated tablet with a score line on one side and plain on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility data. The tablets are packaged in Alu/Alu strips.

The objective of the product development was to obtain a stable and robust formulation of linezolid 150 mg dispersible tablets which is bioequivalent to the WHO recommended comparator product, Zyvox® (linezolid) for oral suspension 100 mg/5 mL (Pharmacia & Upjohn Co. USA). The composition was based on the properties of the active pharmaceutical ingredient and excipients that are used in the comparator product, as well as other excipients that are commonly used in dispersible tablets. Ethyl cellulose, sodium chloride and sodium citrate dihydrate were selected as taste modifiers, while pore forming agents were incorporated to enhance release of the API in the stomach. Sweeteners and flavouring agents were also selected to mask the unpleasant taste of the API. Compatibility studies which were conducted showed that the API was compatible with the selected excipients. Due to the very poor flow properties of linezolid API, a wet granulation process using organic solvents to form light and porous granules was selected to manufacture the finished pharmaceutical product. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), average weight, friability, hardness, loss on drying, disintegration time (NMT 3minutes), fineness of dispersion, uniformity of dosage units (by content uniformity), subdivision of tablets, dissolution (HPLC detection), related substances (HPLC), residual solvents (GC), assay (HPLC) and microbial limits.

Stability testing

Stability studies have been performed 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 appeared to be stable, with no significant change or 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 2021 according to internationally accepted guidelines.

Four tablets as a single dose fasting in-vivo bioequivalence study of Linezolid dispersible tablets 150 mg (Macleods Pharmaceuticals Ltd., India) with 30 mL of Zyvox® (linezolid) for oral suspension 100 mg/5 mL (Pharmacia & Upjohn Co. USA) in healthy, adult, human subjects (study no. BEQ-2556-LINE-2019).

The objective of the study was to compare the bioavailability of the stated Linezolid 150 mg dispersible tablet manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Zyvox® oral suspension (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 – 4 dispersible tables Linezolid 150 mg (linezolid 600 mg) Batch no. RLA2001A.
Treatment R: Reference – 30 ml Zyvox® 100mg/5ml oral suspension (linezolid 600 mg) Batch no. AJ3034.

The dispersible tablets were dispersed in 50 ml water, and after intake, the container was rinsed with 50 ml water, which was additionally administered. The Reference was administered with 50 ml water. A 8 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 300 ng/ml for linezolid.

The study was performed with 24 participants; data generated from a total of 22 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.99 ± 0.67	1.01 ± 0.62	-	-
C_{max} (µg/ml)	14.0 ± 2.3 (13.8)	13.8 ± 2.6 (13.6)	101.3	95.6 – 107.3
AUC_{0-t} (µg.h/ml)	112 ± 26 (109)	110 ± 28 (106)	102.3	97.2 – 107.6
AUC_{0-inf} (µg.h/ml)	115 ± 27 --	114 ± 29 --	-	-

*geometric mean

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 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® oral suspension (Pharmacia & Upjohn Co.).

4. Summary of Product Safety and Efficacy

[TB391 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator product. According to the submitted

data on quality and bioavailability, [TB391 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator product Zyvoxid® oral suspension (Pharmacia & Upjohn Co.) for which benefits have been proven in terms of clinical efficacy.
The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [TB391 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB391 trade name] has been shown to be bioequivalent to Zyvoxid® oral suspension (Pharmacia & Upjohn Co.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB391 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB391 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 has advised that the quality, efficacy and safety of [TB391 trade name] allow inclusion of [TB391 trade name], manufactured at Macleods Pharmaceuticals Limited, Plot No.50 to 54A SEZ, Phase II, Pithampur,Dist.: Dhar, Madhya Pradesh, 454774, India in the list of prequalified medicinal products.