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	[TB321 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited Unit IV, Plot no. 9 & 10 Pharma zone, Phase II Indore special economic zone Pithampur Madhya Pradesh – 454 775 India
Active Pharmaceutical Ingredient(s) (API)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinones antibacterials, (J01XX08)
Therapeutic indication	[TB321 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.* [TB321 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

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

1. Introduction

[TB321 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.

[TB321 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.

[TB321 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*.

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.

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, 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; R-isomer ≤ 0.08%), 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 microcrystalline cellulose, corn starch, sodium starch glycolate, hydroxypropyl cellulose and magnesium stearate. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol and talc. None of the excipients are derived from human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, oval-shaped, biconvex, film-coated tablet, debossed with 'CL' on one side and a central break-line on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in HDPE bottles and PVC-aluminium blisters.

The development of the multisource product was based on the pharmacokinetic and physico-chemical properties known for the WHO recommended comparator product, Zyvox® 600 mg film-coated tablets, which is an immediate release solid dosage form for oral administration. The excipients are qualitatively similar to those of the comparator product. The proposed formulation being high dose and the API being fluffy in nature, the direct compression process was not considered as the method of choice. Similar to the comparator product, the wet granulation method was selected. The product development pathway essentially involved experimentation to reach the prototype formulation composition based on in-vitro dissolution profiles and was then optimized for the critical formulation attributes.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and its polymorphic form (XRPD) and the colorant, average weight, water content (KF), uniformity of dosage units (by mass variation), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), uniformity of weight, disintegration time and microbiological examination. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30^0C/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 with respect to chemical, physical and performance parameters at these storage conditions, with no negative trend observed. No change in the polymorphic form of the API was 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

No bioequivalence study has been performed. As linezolid is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Zyvox® 600 mg tablet (Pfizer Limited) and the test linezolid 600 mg tablet (Cipla Limited, India) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1, 4.5 and 6.8 have been shown. Accordingly, the test tablet [TB321 trade name] (Cipla Limited, India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the reference Zyvox® 600 mg tablet (Pfizer Limited).

4. Summary of product safety and efficacy

[TB321 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [TB321 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Zyvox® 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 [TB321 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB321 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB321 trade name] and reference Zyvox® (Pfizer Limited).can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB321 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [TB321 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 has advised that the quality, efficacy and safety of [TB321 trade name] allow inclusion of [TB321 trade name], manufactured at Cipla Limited, Unit IV, Plot no. 9 & 10, Pharma zone, Phase II, Indore special economic Zone, Pithampur, Madhya Pradesh – 454 775, India in the list of prequalified medicinal products.