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	[TB351 trade name][*]
Manufacturer of Prequalified Product	Celltrion Pharm Inc. 82, 2 Sandan-ro, Ochang-eup Cheongwon-gu, Cheongju-si Chungcheongbuk-do 28117, Republic of Korea
Active Pharmaceutical Ingredients (APIs)	Linezolid
Pharmaco-therapeutic group (ATC Code)	Oxazolidinone antibacterials (J01XX08)
Therapeutic indication	[TB351 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. [TB351 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 (see sections 4.2, 4.4 and 5.1). Consideration should be given to official treatment guidelines for tuberculosis, e.g. those of WHO.

1. Introduction

[TB351 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.

[TB351 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.

[TB351 trade name] should be initiated 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)

Linezolid

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. 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 and XRPD), loss on drying, specific optical rotation, sulphated ash, heavy metals, assay (HPLC), related substances (HPLC), R-Isomer content (HPLC), residual solvents (GC), synthetic impurities (GC, HPLC), particle size distribution and microbial limit tests. 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 hydroxypropyl cellulose low-substituted, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, colloidal silicon dioxide and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide and macrogol/ polyethylene glycol. TSE/BSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white oval shaped, film- coated tablet with score line on both sides and debossed with 'CC' on one side. The score-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 PVC/PVDC-Alu blister pack and HDPE bottle with polypropylene child resistant closure and heat seal liner.

The goal of the formulation development was to develop a product which is therapeutically equivalent to the WHO recommended comparator product, Zyvox® 600 mg film-coated tablets. The formulation development was based on the evaluation of API properties, characterisation of the comparator product and API-excipient compatibility studies. Due to the potential risk on low content uniformity resulting from low flowability of linezolid during direct compression, wet granulation was selected as the manufacturing process.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and visual test for titanium dioxide, dissolution (HPLC detection), uniformity of dosage units (by weight variation), assay (HPLC), related substances (HPLC), water content, microbial limit test and polymorphic form (XRPD). 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

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 (Pharmacia) and the test Linezolid 600 mg tablet (Celltrion, Republic of Korea) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 has been shown. Accordingly, the test tablet Linezolid 600 mg tablet (Celltrion, Republic of Korea) meets the criteria for a BCS-based biowaiver and is therefore considered bioequivalent to the reference Zyvox® 600 mg tablet (Pharmacia).

4. Summary of Product Safety and Efficacy

[TB351 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB351 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [TB351 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB351 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB351 trade name] and Zyvox® 600 mg tablet (Pharmacia) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB351 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 [TB351 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. [TB351 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 [TB351 trade name] allow inclusion of [TB351 trade name], manufactured at Celltrion Pharm Inc., 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongiu-si, Chungcheongbuk-do, 28117, Republic of Korea, in the list of prequalified medicinal products.