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	[TB403 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Area, Chikalthana Chhatrapati Sambhajinagar – 431210 Maharashtra State India
Active Pharmaceutical Ingredient(s) (API)	Pretomanid
Pharmaco-therapeutic group (ATC Code)	Other drugs for treatment of tuberculosis J04AK08
Therapeutic indication	[TB403 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* in adults and adolescents at least 14 years old.

1. Introduction

[TB403 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* in adults and adolescents at least 14 years old.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

Treatment with pretomanid should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium 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)

Pretomanid is a white to off-white to yellow, non-hygroscopic powder. It has poor solubility across the physiological pH range and therefore considered critically insoluble according to the WHO PQT/MED's classification.

The APIMF of linezolid has been accepted through WHO's APIMF procedure. Details pertaining to manufacturing process development of Pretomanid API has been provided in the restricted part of the API master file. Pretomanid manufactured by the API manufacturer is the S-isomer. Pretomanid

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

exhibits polymorphism; the API manufacturer consistently produces crystalline form-I which is stable.

The API specifications include tests for description, solubility, identification (IR, HPLC), powder x-ray diffraction, water determination, residue on ignition, limit of R-isomer (HPLC), assay (HPLC), organic impurities (HPLC), potential genotoxic impurities (GC-MS), residual solvents (GC), microbial limits and particle size distribution.

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, microcrystalline cellulose, sodium starch glycolate, povidone, sodium lauryl sulfate, colloidal silicon dioxide and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. Magnesium stearate is of vegetable origin. TSE/BSE compliance declarations have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, oval, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet is plain on both sides. The tablets are packaged in clear PVC/PVDC-alu blister cards and HDPE bottle packs.

The objective of the formulation development was to obtain a product which is bioequivalent to the WHO recommended comparator product, Pretomanid 200 mg tablets (Mylan Laboratories Limited). The comparator product was characterized and on that basis a quality target product profile was defined, and critical quality attributes were identified. Selection of excipients was based on excipients used in the comparator product, scientific literature and API-excipient compatibility data. Considering the high content of the API and its physical characteristics as well as ensuring satisfactory flow property of the granular blend and uniformity of dosage units, wet granulation was selected as the manufacturing process of the tablets. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. 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 by HPLC (UV; PDA/DAD detection), water content (KF), dissolution (HPLC detection), uniformity of content, assay (HPLC), degradation products (HPLC) and microbial limits. 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 2022/2023 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study comparing [TB403 trade name] manufactured by Lupin Limited, India with Pretomanid tablets 200 mg manufactured by Mylan Laboratories Limited, Hyderabad - 500 096, India manufactured for Mylan Specialty L.P. Morgantown, WV 26505 U.S.A. 8117880 in healthy, adult, human female subjects under fed conditions (study no. SLS-CL-0041-22-PRET).

The objective of the study was to compare the bioavailability of the stated [TB403 trade name] manufactured by/for Lupin Limited, India (test drug) with the reference formulation Pretomanid 200 mg tablet (Mylan Laboratories Limited) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy adult female subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet [TB403 trade name] (pretomanid 200 mg) Batch no. A290078.
Treatment R:	Reference – 1 tablet Pretomanid 200 mg (pretomanid 200 mg) Batch no. 8117880.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 120h post dose) were taken during each study period to obtain bioavailability characteristics AUC_{0-t}, and C_{max} for bioequivalence evaluation. Drug concentrations for pretomanid were analyzed using a validated LC-MS/MS method. The limit of quantification (LQC) was stated to be about 14.956 ng/mL for pretomanid.

The study was performed with 32 participants; data generated from a total of 31 subjects were utilized for pharmacokinetic and statistical analysis and to establish bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for pretomanid as well as statistical results are summarised in the following table

Pretomanid

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)	6.02 ± 2.23	5.21 ± 1.04	–	–
C_{max} (ng/mL)	2235 ± 475 (2188)	2546 ± 518 (2498)	87.6	84.3 – 91.1
AUC_{0-t} (ng·h/mL)	108508 ± 25893 (105893)	117786 ± 20689 (115801)	91.4	88.3 – 94.7
AUC_{0-inf} (ng·h/mL)	127939 ± 39556 –	136237 ± 27814 –	–	–

The results of the study showed that preset bioequivalence acceptance limits of 80 – 125 % are met by both AUC and Cmax values regarding pretomanid. Accordingly, the test [TB403 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Pretomanid 200 mg tablet (Mylan Laboratories Limited).

4. Summary of product safety and efficacy

[TB403 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, [TB403 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Pretomanid 200 mg tablets (Mylan Laboratories Limited) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB403 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 [TB403 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB403 trade name] has been shown to be bioequivalent with Pretomanid 200 mg tablets (Mylan Laboratories Limited) healthy, adult, human female subjects under fed condition.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB403 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 [TB403 trade name] was acceptable for the following indication: 'in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* in adults and adolescents at least 14 years old', and would allow inclusion of [TB403 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Chhatrapati Sambhajinagar – 431210, Maharashtra State, India in the list of prequalified medicinal products.