This part reflects 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:	[TB352 trade name]*
Manufacturer of Prequalified Product:	Micro Labs Limited (Unit-03) 92, Sipcot Industrial Complex Hosur-635126 Tamil Nadu India
Active Pharmaceutical Ingredient (API):	Ethionamide
Pharmaco-therapeutic group **(ATC Code):**	Antimycobacterial (J04AD03)
Therapeutic indication:	[TB352 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB352 trade name] is only used as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

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

1. Introduction

[TB352 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* Ethionamide is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

[TB352 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 (APIs)

Ethionamide has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides assurance that ethionamide, used in the manufacture of [TB352 trade name], is of good quality and manufactured in accordance with WHO good manufacturing practices. API prequalification consists of a comprehensive evaluation procedure that has two components: assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Data submitted show that ethionamide is not BCS highly soluble, thus particle size distribution limits were included in the FPP manufacturer's API specifications, based on the data obtained for the API batch used in the manufacture of the bio-batch.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, povidone, polysorbate, colloidal anhydrous silica, pineapple flavour, sucralose and magnesium stearate. BSE/TSE free certificates are provided from suppliers of all excipients. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow-coloured, circular, flat-faced, bevelled edge, uncoated dispersible tablet, debossed with "E" above "125" on one face and plain on the other face. The tablets are presented in clear PVC/PE/PVdC-Alu blisters and plain Alu-Alu strip packs.

The development of the final composition of product has been described. The aim was to develop a stable product suitable for paediatric use, which would be bioequivalent to the WHO recommended comparator product, Trecator®250 mg Tablets. The selection of the excipients was based on known functional characteristics, the information on the comparator product and compatibility with the API. Sucralose and pineapple flavour were selected as sweetener and flavouring agent respectively for this paediatric formulation. Wet granulation was selected for the manufacture of the tablets in view of its conventional acceptability and robustness. Optimization trials were carried out at different levels during development in order to obtain a tablet with the desired physical characteristics, including dissolution profiles. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications, regarded adequate for control of the product, include tests for appearance; identification of the API (IR and HPLC); average mass; tablet dimensions; disintegration time; resistance to crushing; friability; water content (KF); fineness of dispersion; uniformity of dosage units (by mass variation); dissolution (UV detection); assay (HPLC); related substances (HPLC); and microbial limits. The test procedures 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 40°C/75%RH as accelerated conditions, in each packaging configuration 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 Bio-Equivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

An open label, randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of 2 tablets of Ethionamide dispersible tablets 125 mg (2x125 mg) (Test) of Micro Labs Limited, India and 1 tablet of Trecator® (ethionamide tablets, USP) tablets 250 mg (Reference) of Norwich Pharmaceuticals, Inc. North Norwich, New York 13814, in healthy, adult, human subjects under fasting conditions (Study no. 404-16).

The objective of the study was to compare the bioavailability of the stated Ethionamide 125 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Trecator® (Wyeth Pharmaceuticals) 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 – 2 dispersible tablets Ethionamide 125 mg (ethionamide 250 mg) Batch no. EDAEH0001
Treatment R:	Reference – 1 tablet Trecator® (ethionamide 250 mg) Batch no. 462329

The test tablet was dispersed in 50 mL water before intake. The reference tablet was taken with 240 mL water. A 13-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 24 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethionamide were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/mL for ethionamide.

The study was performed with 36 participants. Data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)[#]	1.13 (0.17 – 3.0)	0.83 (0.25 – 3.5)	-	-
C_{max} (ng/mL)	2669 ± 1063 (2484)	2747 ± 1117 (2537)	97.9	85.5 – 112.2
AUC_{0-t} (ng.h/mL)	8865 ± 1809 (8672)	9003 ± 2156 (8723)	99.4	94.8 – 104.3
AUC_{0-inf} (ng.h/mL)	9027 ± 1837 --	9188 ± 2184 --	-	-

*geometric mean; [#]median (range)

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ethionamide. Accordingly, the test Ethionamide 125 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Trecator® (Wyeth Pharmaceuticals).

4. **Summary of Product Safety and Efficacy**

[TB352 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, [TB352 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator products Trecator® 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 [TB352 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB352 trade name] has shown to be bioequivalent with Trecator® (Wyeth Pharmaceuticals, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB352 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 [TB352 trade name] was acceptable for the following indication: **"indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*"** and has advised that the quality, efficacy and safety of [TB352 trade name] allow inclusion of [TB352 trade name], manufactured at Micro Labs Limited (Unit-03), 92, Sipcot Industrial Complex, Hosur - 635126, Tamil Nadu, India, in the list of prequalified medicinal products.