This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Ethionamide 250 mg Tablets*
Manufacturer of Prequalified Product:	Micro Labs Limited (Unit: ML-03) 92, Sipcot Industrial Complex Hosur – 635126 Tamilnadu INDIA
Active Pharmaceutical Ingredient (API):	Ethionamide
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial (J04AD03)
Therapeutic indication:	Ethionamide 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.

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Ethionamide 250 mg Tablets 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.

Ethionamide 250 mg Tablets should be prescribed by a physician experienced in the management of tuberculosis infection.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

The APIMF of ethionamide, 2-ethylpyridine-4-carbothioamide, has been accepted through WHO's APIMF procedure. The API is yellow coloured, achiral, non-hygroscopic and practically insoluble in water. The solubility increases with decreasing pH. It is manufactured in several steps from 4-cyanopyridine. The manufacturing process consistently produces one crystal form.

Ethionamide, described in the Ph.Int., Ph.Eur. and USP, is considered well established.

The API specifications, which are pharmacopoeial based, include tests for appearance, solubility, identification, appearance of solution, acidity, related substances (HPLC and TLC), heavy metals, loss on drying, sulphated ash, assay, residual solvents, particle size distribution, bulk density and microbiological quality.

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 colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone and sodium starch glycolate. The tablet coat contains FD&C yellow #6/sunset yellow FCF aluminium lake, hypromellose, polyethylene glycol, talc and titanium dioxide. None of these ingredients are of animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
Ethionamide 250mg Tablets are orange coloured, circular, biconvex film-coated tablets plain on both faces. The tablets are packaged in white opaque PVDC/PVC/Alu blisters and in white round HDPE bottles with CRC cap.

The development of the final composition of product has been described. The aim was to develop a stable product, which would be bioequivalent to the comparator product, Trecator®. The selection of the excipients was based on known functional characteristics, the information on the comparator product and compatibility with the API. Studies were performed to select the appropriate particle size distribution of the API, which is of BCS low solubility. Direct compression did not result in tablets of acceptable physical properties and the wet granulation was selected for the manufacture of the core tablets. 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. Validation data demonstrated the consistency of the process.

Specifications
The finished product specifications include tests for appearance, identification of the API (IR and HPLC), average mass, uniformity of dosage units (by mass variation), dissolution (UV detection), water content, related substances (HPLC), assay (HPLC), residual solvents and microbial limits.

Stability testing
Stability studies have been conducted in each packaging configuration at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions. The product proved to be quite stable at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2011 according to internationally accepted guidelines.

A randomized, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Ethionamide USP 250 mg tablets of Micro Labs Ltd., with Trecator® (ethionamide tablets, USP) 250 mg tablets of Wyeth Pharmaceuticals Inc., in normal, healthy, adult, male and female human subjects under fasting condition (study no. ARL/11/021)

The objective of the study was to compare the bioavailability of the stated Ethionamide 250 mg tablet manufactured by Micro Labs Ltd., India (test drug) with the same dose of the reference formulation (Trecator®, Wyeth Pharmaceuticals Inc.) 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 – 1 tablet Ethionamide 250 mg (ethionamide 250 mg) Batch no. ETAEH0005.
Treatment R:	Reference – 1 tablet Trecator® (ethionamide 250 mg) Batch no. 435406.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 18 samples within 24 h 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 48 participants; data generated from a total of 47 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 summarized in the following tables:

Ethionamide

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)	1.08 ± 0.55	1.16 ± 0.70	-	-
C_{max} (µg/ml)	2.26 ± 0.47 (2.22)	2.36 ± 0.53 (2.30)	96.3	90.0 – 103.1
AUC_{0-t} (µg.h/ml)	8.46 ± 1.63 (8.31)	8.56 ± 1.62 (8.41)	98.8	95.5 – 102.2
AUC_{0-inf} (µg.h/ml)	8.70 ± 1.68 (8.54)	8.80 ± 1.67 (8.63)	98.9	95.7 – 102.3

* 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 ethionamide. Accordingly, the test tablet Ethionamide 250 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Trecator® (Wyeth Pharmaceuticals Inc.).

4. Summary of Product Safety and Efficacy

Ethionamide 250 mg Tablets 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, Ethionamide 250 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Trecator® (ethionamide 250 mg film-coated tablets) 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 Ethionamide 250 mg Tablets is used in accordance with the SmPC.

Bioequivalence

Ethionamide 250 mg Tablets has shown to be bioequivalent with Trecator® (ethionamide 250 mg film-coated tablets, Wyeth Pharmaceuticals Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, Ethionamide 250 mg Tablets 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 Ethionamide 250 mg Tablets was acceptable for the following indication: **"as a second-line antimycobacterial drug 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 Ethionamide 250 mg Tablets, allow inclusion of Ethionamide 250 mg tablets manufactured at Micro Labs Limited (Unit: ML-03), 92, Sipcot Industrial Complex, Hosur – 635126, Tamilnadu, India in the list of prequalified medicinal products.