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	[TB133 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited, Unit 2, Plot No. 25-27 Survey No. 366 Premier Industrial Estate Kachigam Daman 396 210 India
Active Pharmaceutical Ingredient(s) (API)	Ethionamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AD03)
Therapeutic indication	[TB133 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

1. Introduction

[TB133 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.

[TB133 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients and in patients with severe liver impairment.

It is recommended that therapy is given only on the advice of a tuberculosis experienced physician.

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)

Ethionamide, 2-ethyl-4-pyridinecarbothioamide, is official in the Ph.Int., USP and Ph.Eur. and well established. Ethionamide manufactured by the approved API supplier meets pharmacopoeia specifications. Additional specifications include determination of residual solvents, palladium – used as catalyst – and related substances with HPLC.

Long-term stability data at 30°C/70%RH and accelerated stability data provided for three (3) batches of ethionamide API, manufactured by the approved supplier, showed neither visible variability nor

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

change over time, confirming the stability of the API. A two-year retest period was approved for ethionamide API packed in double LDPE bags kept in HDPE drums.

Other ingredients

Other ingredients used in the tablet formulation include maize starch, gelatine, sodium starch glycollate, colloidal anhydrous silica, gum acacia, purified talc, magnesium stearate, povidone, hypromellose, titanium dioxide, color Quinoline Yellow and diethylphthalate. Magnesium stearate is from plant origin, while a certification (CEP) with respect to the BSE/TSE free status of gelatine has been provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[TB133 trade name] are yellow circular, deep biconvex film coated tablets. [TB133 trade name] are packed in aluminium/aluminium strip packs and a bulk pack of 100 tablets in sealed polybag/triple laminated bag packed with a silica gel bag in a HDPE jar with a taggered seal.

The development of the final composition has been described. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three production scale batches demonstrated the consistency of the process and the quality of the product.

Stability testing

Stability studies have been performed at 25ºC/60%RH (zone II) as long-term conditions and at accelerated conditions. At the time of the prequalification, a provisional shelf-life of 24 months has been allowed for [TB133 trade name]. The applicant committed to continue long-term testing on production scale batches for a period of time sufficient to cover the whole proposed shelf-life and to report any out-of-specification results immediately to WHO.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2006 according to internationally accepted guidelines.

An open label, randomized, two-treatment, two sequence, two period, two way crossover, single dose bioequivalence study of [TB133 trade name] manufactured by Macleods Pharmaceuticals Limited, India comparing with Trecator® tablet (each containing ethionamide 250 mg) manufactured by OSG Norwich Pharmaceuticals Inc. Norwich, New York for Wyeth Pharmaceuticals Inc. Philadelphia, PA in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-051-ETHI-2006).

The objective of the study was to compare the bioavailability of the stated ethionamide tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of reference tablet and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – [TB133 trade name] (ethionamide 250 mg) Batch No. EC601
Treatment R:	Reference – Trecator® 250 mg (film-coated) tablets (ethionamide 250 mg) Batch No. 425051

An 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 method. The limit of quantification was stated to be 25.7 ng/mL.

The study was performed with 40 participants, data generated from a total of 40 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Geometric means (AUC, C_{max}) and arithmetic means (t_{max}) for ethionamide as well as statistical results are summarised in the following tables:

Ethionamide

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)	0.966 ± 0.638	0.970 ± 0.725	–	–
C_{max} (ng/mL)	2489 ± 752 (2371)	2547 ± 860 (2434)	97.4	87.9 – 108.0
AUC_{0-t} (ng·h/mL)	8941 ± 2171 (8698)	8791 ± 1779 (8619)	100.9	95.9 – 106.2
AUC_{0-inf} (ng·h/mL)	9161 ± 2161 (8925)	8951 ± 1777 (8782)	101.6	96.7 – 106.8

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding ethionamide. Accordingly, the test product [TB133 trade name] (Macleods Pharmaceuticals Ltd., India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Trecator® (ethionamide 250 mg film-coated tablets).

4. Summary of product safety and efficacy

[TB133 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, [TB133 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Trecator® tablet (OSG Norwich Pharmaceuticals Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB133 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 [TB133 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB133 trade name] has been shown to be bioequivalent with Trecator® tablet (OSG Norwich Pharmaceuticals Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB133 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 [TB133 trade name] 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 would allow inclusion of [TB133 trade name], manufactured at Macleods Pharmaceutical Limited, Plot No. 25-27, Survey No. 366, Premier Industrial Estate Kachigam 396210 Daman, India in the list of prequalified medicinal products.