

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Ethionamide 250 mg Tablets*
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited, Andheri East, Mumbai, India
Active Pharmaceutical Ingredient (API):	Ethionamide
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial (J04AD03)
Therapeutic indication:	Ethionamide 250 mg Tablets is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by <i>Mycobacterium tuberculosis</i> . 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 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 according to SOP 20 of the WHO Prequalification programme.

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 pharmacopoeial 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 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, gelatin, sodium starch glycolate, 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

Ethionamide 250mg tablets are yellow circular, deep biconvex film coated tablets. Ethionamide 250mg tablets 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 tagged 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 25°C/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 Ethionamide 250mg tablets. 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.

Conclusions

The quality part of the dossier is accepted

3. Assessment of Bio-Equivalence

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 Ethionamide tablet (each containing ethionamide 250 mg) manufactured by Macleods Pharmaceuticals Ltd., 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 – Ethionamide 250 tablets
(ethionamide 250 mg)
Batch No. EC601
- Treatment R: Reference – Trecator® 250 mg (film-coated) tablets
(ethionamide 250 mg)
Batch Nos. 425051

A 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) arithm.mean ± SD (*)	Reference (R) arithm. mean ± SD (*)	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

* geometric mean

Conclusions

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 product Ethionamide 250 mg tablets (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

Ethionamide 250 mg Tablets has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference product, Trecator[®] (ethionamide 250 mg film-coated tablets).

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

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

Efficacy and Safety

Regarding clinical efficacy and safety, Ethionamide 250 mg Tablets are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics is taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus 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 to include Ethionamide 250 mg Tablets, manufactured at Macleods Pharmaceuticals Limited, Plot No. 25-27, Survey No. 366, Premier Industrial Estate Kachigam 396210 Daman, India in the list of prequalified medicinal products.