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	[TB333 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited, Phase II, Unit II, Plot No 25-27, Survey No 366, Premier Industrial Estate Kachigam, Daman, 396 210, India
Active Pharmaceutical Ingredient (API)	Ethionamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AD03)
Therapeutic indication	[TB333 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB333 trade name] is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed

1. Introduction

[TB333 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.

[TB333 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 (API)

Ethionamide, 2-ethylpyridine-4-carbothioamide, is yellow coloured, achiral and non-hygroscopic substance, practically insoluble in water. The API is described in the Ph.Int, Ph.Eur and USP and is considered well established in the WHO PQTm programme.

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

The pharmacopoeial based API specifications include tests for description, solubility, identification, appearance of solution, acidity, related substances (HPLC and TLC), heavy metals, loss on drying, sulfated ash, assay, residual solvents, particle size distribution (PSD) and palladium content.

The API is of BCS low solubility, hence PSD is considered a critical parameter for the FPP. The PSD acceptance criteria were set on the information of the API lot used in the FPP biobatch.

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 tablet formulation include crospovidone, microcrystalline cellulose, sucralose, corn starch, povidone, peppermint flavour, low substituted hydroxypropyl cellulose, sodium chloride, aspartame, menthol, colloidal anhydrous silica 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, biconvex, uncoated tablet having an angular break line on one side and plain surface on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in Alu-Alu strip packs.

The development of the composition of the dispersible tablets, targeted towards the paediatric population, has been described. The selection of excipients was based on their suitability to achieve the desired characteristics of the dispersible tablet and their compatibility with ethionamide. Sucralose and aspartame were selected as sweeteners to mask unpleasant tastes, with sodium chloride as taste enhancer. Peppermint and menthol are included as flavouring agents to mask the unpleasant, characteristic sulfur odour, of ethionamide. A full factorial design has been used for optimization of sweetening agents, flavouring agent and taste enhancer against organoleptic perception of the product.

The compressibility index as determined from the bulk density and the tapped density indicated that ethionamide exhibits poor flow properties. Thus a wet granulation strategy was explored to obtain better flow properties and uniformity of the API. The target was to develop the dispersible tablets matching the dissolution profile of the WHO recommended comparator product, Trecator® 250 mg tablets. 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 description, identification of the API (HPLC, UV), average weight, friability, hardness, disintegration time (≤ 3 minutes), fineness of dispersion, loss on drying, uniformity of dosage units (by weight variation), dissolution (UV detection), related substances (HPLC), assay (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 the packaging 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 2015 according to internationally accepted guidelines.

Study title: Bioequivalence study of two tablets as single dose of [TB333 trade name] manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Trecator® (ethionamide USP) tablets 250 mg manufactured for Wyeth Pharmaceuticals Inc. USA in healthy, adult, human subjects under fasting condition (study no. BEQ-1561-ETHI-2015).

The objective of the study was to compare the bioavailability of the stated [TB333 trade name] manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with 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 treatments in a randomized fashion:

Treatment T:	Test – 2 tablets [TB333 trade name] (ethionamide 250 mg) Batch no. EEC1502A
Treatment R:	Reference – 1 tablet Trecator® (ethionamide 250 mg) Batch no. 456518

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 16 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 35 participants; data generated from a total of 28 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:

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)	0.46 ± 0.17	0.75 ± 0.45	-	-
C_{max} (ng/mL)	3584 ± 1002 (3444)	3332 ± 1100 (3165)	108.8	98.3 – 120.5
AUC_{0-t} (ng.h/mL)	9121 ± 2055 (8892)	9162 ± 2032 (8930)	99.6	95.5 – 103.8
AUC_{0-inf} (ng.h/mL)	9281 ± 2080 (NA#)	9321 ± 2035 (NA#)	--	--

* geometric mean; #not analyzed

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 [TB333 trade name] meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Trecator® (Wyeth Pharmaceuticals Inc.).

4. Summary of product safety and efficacy

[TB333 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, [TB333 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Trecator® (Wyeth Pharmaceuticals Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB333 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 [TB333 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB333 trade name] has been shown to be bioequivalent with Trecator® 250 mg tablet (Wyeth Pharmaceuticals Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB333 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 [TB333 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 [TB333 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II, Unit II, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 396 210, India in the list of prequalified medicinal products.