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	[TB239 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited (Unit: 03) 92, Sipcot Industrial Complex Hosur – 635126 Tamilnadu India
Active Pharmaceutical Ingredient (API)	Protionamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial, thiocarbamide derivatives (J04AD01)
Therapeutic indication	[TB239 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children.

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

1. Introduction

[TB239 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children.
[TB239 trade name] is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.
[TB239 trade name] should be initiated by a health care provider experienced in the management of tuberculosis infection.

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)

Protionamide (, 2-propylthioisonicotinamide, is described in the Ph.Int.

The APIMF 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 two chemical steps from 4-cyanopyridine, followed by a purification step. The manufacturing process consistently produces one crystal form.

The API specifications include tests for appearance, solubility, identification, acidity, melting point, heavy metals, loss on drying, sulphated ash, assay, related substances (HPLC), residual solvents, particle size distribution, bulk density and microbial limits.

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 in the core tablet formulation include colloidal anhydrous silica, croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, polysorbate 80 and povidone. The tablet coat contains FD&C yellow #6/sunset yellow FCF Aluminium Lake, hypromellose, polyethylene glycol, talc and titanium dioxide. BSE/TSE-free certification has been provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an orange coloured, circular biconvex, film-coated tablet with score on one face and plain on the other. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in white opaque PVC/PVdC-Alu blisters and in HDPE bottles with child-resistant 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, Peteha®(film-coated tablets containing 250 mg protionamide), manufactured by Fatol Arzneimittel, Germany. The selection of the excipients was based on known functional characteristics, information on the comparator product and compatibility with the API. The direct compression approach was not feasible with respect to compressibility and the wet granulation process 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.

Product 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), disintegration time, dissolution (UV detection), water content, assay (HPLC), related substances (HPLC), residual solvents, subdivision of tablets and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/60% RH and 30°C/65% RH as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at all storage conditions in both packaging configurations. 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 2010 according to internationally accepted guidelines.

A randomized, open label, balanced, two-sequence, two-treatment, two-period, single dose, crossover bioequivalence study of Protionamide tablets 250 mg manufactured by Micro Labs Ltd., with Peteha® (protionamide tablets 250 mg) manufactured by Fatol Arzneimittel, Germany, in normal, healthy, adult, male human subjects under fasting condition (study no. ARL/10/320).

The objective of the study was to compare the rate and extent of absorption of the stated protionamide 250 mg tablets with the same dose of Peteha® 250 mg tablets. The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T:	Test – Protionamide 250 mg tablets (protionamide 250 mg) Batch no. PTAHH0004
Treatment R:	Reference – Peteha® 250 tablets (protionamide 250 mg) Batch no. 022078

A 9 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 14 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC_{inf}, AUC_{0-t}, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for protionamide in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 25 ng/mL for protionamide.

The study was performed with 56 participants, data generated from a total of 53 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (± sd), geometric means (AUC, C_{max}) for protionamide as well as statistical results are summarised in the following table:

Protionamide

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)	1.20 ± 0.62	1.24 ± 0.75	-	-
C_{max} (ng/mL)	1729 ± 768 (1611)*	1878 ± 682 (1783)*	90.4	82.1 – 99.5
AUC_{0-t} (ng.h/mL)	5661 ± 1679 (5443)*	5843 ± 1634 (5644)*	96.4	92.8 – 100.2
AUC_{0-inf} (ng.h/mL)	5821 ± 1719 (5601)*	5996 ± 1654 (5800)*	96.6	92.9 – 100.3

* geometric mean

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding protionamide. Accordingly, the test product Protionamide 250 mg Tablets (Micro Labs Ltd., India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Peteha® 250 mg tablets (Fatol Arzneimittel).

4. Summary of product safety and efficacy

[TB239 trade name] 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 [TB239 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Peteha® for which benefits have been proven in terms of clinical efficacy.

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 [TB239 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB239 trade name] has shown to be bioequivalent with Peteha® (Fatol Arznemittel GmbH, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, 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 [TB239 trade name] was acceptable for the following indication:**" in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children**" and has advised that the quality, efficacy and safety of [TB239 trade name] allow inclusion of [TB239 trade name], manufactured at Micro Labs Limited (Unit: 03), 92, Sipcot Industrial Complex, Hosur – 635126, Tamilnadu, India in the list of prequalified medicinal products.