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	[TB206 trade name]*
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Industrial Area, Chikalthana Aurangabad-431210 India
Active Pharmaceutical Ingredient(s) (API)	Protionamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, thiocarbamide derivatives (J04AD01)
Therapeutic indication	[TB206 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 weighing 10 kg or more.

1. Introduction

[TB206 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 weighing 10 kg or more.

[TB206 trade name] is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

[TB206 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 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.

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

The API specifications include tests for description, solubility, identification, acidity, melting point, heavy metals, loss on drying, sulfated ash, assay, related substances (HPLC), residual solvents, particle size distribution 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 dibasic calcium phosphate dihydrate, povidone, sodium starch glycolate, corn (maize) starch, propylene glycol, sodium benzoate, microcrystalline cellulose, talc, colloidal silicon dioxide and magnesium stearate. The tablet coat contains hypromellose, polyethylene glycol, talc, titanium dioxide and lake of quinoline yellow. BSE/TSE-free certification has been provided for all excipients.

Finished pharmaceutical product (FPP)

The multisource product is a yellow-coloured circular, bevelled edged, biconvex film coated tablet, plain on both sides. The primary pack is a polyethylene bag which is placed in HDPE bottle having polyethylene plain screw cap and aluminium tagger seal.

Pharmaceutical development and manufacture

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). The critical quality attributes and compatibility of the API with the proposed excipients were investigated. Since the API showed poor flow properties, the aqueous wet granulation process was selected for the manufacture of the core tablets. The composition and process parameters were optimised to obtain tablets of desired characteristics. 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 description, identification of the API (IR and UV) and colorants, average weight, uniformity of weight, tablet dimensions, loss on drying, dissolution, assay (HPLC), related substances (HPLC), residual solvents and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/65%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at all storage conditions. 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 2009 according to internationally accepted guidelines:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, pivotal bioequivalence study of Protionamide 250 mg film coated tablets of Lupin Limited, India with Peteha® (protionamide) 250 mg film coated tablets of Fatol Arznemittel GmbH, 66573 Schiffweiler in 36 healthy human adult male subjects, under fasting conditions. (study no. 011-09).

The objective of the study was to compare the bioavailability of the stated Protionamide 250 mg tablet manufactured by Lupin Limited, India (test drug) with the same dose of the reference formulation (Peteha®, Fatol Arznemittel GmbH) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male 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 Protionamide 250 mg (protionamide 250 mg) Batch no. DH88009.
Treatment R: Reference – 1 tablet Peteha® (protionamide 250 mg) Batch no. 022078.

A 7 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 protionamide were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 31 ng/mL for protionamide.

The study was performed with 36 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for protionamide as well as statistical results are summarised in the following tables:

Protionamide

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)	1.19 ± 0.79	1.13 ± 0.72	-	-
C_{max} (ng/mL)	1385 ± 510 (1294)	1400 ± 516 (1318)	98.2	89.6 – 107.6
AUC_{0-t} (ng·h/mL)	4357 ± 1445 (4088)	4321 ± 1393 (4099)	99.7	93.3 – 106.6
AUC_{0-inf} (ng·h/mL)	4497 ± 1450 (4238)	4462 ± 1398 (4244)	99.9	93.7 – 106.4

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 tablet Protionamide 250 mg film-coated tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Peteha® (Fatol Arznemittel GmbH).

4. Summary of product safety and efficacy

[TB206 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, [TB206 trade name] is pharmaceutically and therapeutically equivalent and thus

interchangeable with the comparator product Peteha® (Fatol Arznemittel GmbH for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB206 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 [TB206 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB206 trade name] has been shown to be bioequivalent with Peteha® (Fatol Arznemittel GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB206 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 [TB206 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 weighing 10 kg or more ', and would allow inclusion of [TB206 trade name], manufactured at Lupin Ltd, A-28/1, MIDC Industrial Area, Chikalthana, Aurangabad-431210, India in the list of prequalified medicinal products.