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	[TB243 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase II/ Phase III, Unit II, Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210, India Telephone: + 91 0260 2244337 Fax: + 91 0260 2241565
Active Pharmaceutical Ingredient (API)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK01)
Therapeutic indication	[TB243 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB243 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*
[TB243 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, severe liver impairment or acute gout.
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)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified pyrazinamide (up to 500mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble.

Pyrazinamide is described in the Ph.Int., Ph.Eur. and the USP and is considered well-established in the WHO PQP.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, appearance of solution, acidity or alkalinity, related substances (TLC and HPLC), heavy metals, sulfated ash, water content, assay and particle size distribution.

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.

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

Other ingredients

Other ingredients used in the tablet formulation include colloidal anhydrous silica, magnesium stearate, maize starch, povidone, purified talc and sodium starch glycolate. Magnesium stearate is of vegetable origin.

Finished pharmaceutical products (FPP)

Pharmaceutical development and manufacture

[TB243 trade name] is white, circular, flat, bevelled edged, uncoated tablets, having 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 PVC-aluminium blister packs of 10 or 28 tablets. Bulk packs contain 1000 tablets in an LDPE bag, packed in an opaque HDPE container, sealed with aluminium tagger seal and closed with a screw thread polypropylene closure.

An acceptable product quality review has been provided on the basis that the product is well-established and hence formulation development studies are not needed in the dossier.This is in accordance with WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

For manufacture of the tablets a conventional wet granulation process was selected. The multisource and comparator products showed very rapid dissolution 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 are pharmacopoeial based and include tests for description, identification, average weight, friability, hardness, uniformity of dosage units (by mass variation), loss on drying, dissolution, related substances (HPLC and TLC), assay and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions for tablets presented in all accepted packaging configurations. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. 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 2005 according to internationally accepted guidelines.

An open label, randomised, two-treatment, two sequence, two period, two-way crossover, single dose bioequivalence study of Pyrazinamide tablets (each containing pyrazinamide 500 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Rolab-pyrazinamide 500 tablets (each containing pyranizamide 500 mg) of Rolab Pvt. Ltd. (Novartis South Africa) in healthy, adult, male, human subjects under fasting conditions (study BEQ-010-PYRA-2005).

The objective of the study was to compare the rate and extent of absorption of the stated pyrazinamide 500 mg tablets with the same dose of Rolab-Pyrazinamide 500 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 – Pyrazinamide 500 mg tablets (pyrazinamide 500 mg) Batch no. PI501

Treatment R: Reference – Rolab-Pyrazinamide 500 tablets
(pyrazinamide 500 mg)
Batch no. 135097

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 17 samples within 72 h 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 pyrazinamide in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 0.6 µg/mL for pyrazinamide.

The study was performed with 24 (+ 4 standby) participants, data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Pyrazinamide

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)	1.61 ± 0.94	1.35 ± 1.14	-	-
C_{max} (µg/mL)	9.41 ± 2.62 (9.07)	9.43 ± 2.35 (9.17)	98.9	92.9 – 106.2
AUC_{0-t} (µg·h/mL)	98.9 ± 32.2 (93.2)	97.9 ± 25.5 (94.2)	98.9	91.3 – 107.2
AUC_{0-inf} (µg·h/mL)	114.1 ± 31.1 (109.9)	114.1 ± 24.7 (111.4)	98.6	92.1 – 105.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding pyrazinamide. Accordingly, the test product Pyrazinamide 500 mg tablets (Macleods Pharmaceutical Ltd., India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Rolab-Pyrazinamide 500 mg tablets (Novartis).

4. Summary of Product Safety and Efficacy

[TB243 trade name] 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 products, Rolab-Pyrazinamide 500 mg tablets (Novartis).

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

[TB243 trade name] has shown to be bioequivalent with Rolab-Pyrazinamide 500 mg tablets (Novartis).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB243 trade name] is 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 [TB243 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*"** and has advised that the quality, efficacy and safety of [TB243 trade name] allow inclusion of [TB243 trade name] , manufactured at Macleods Pharmaceuticals Limited, Phase II/ Phase III, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate Kachigam, Daman – 396210, India in the list of prequalified medicinal products.