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	[TB159 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceutical Limited Unit II, Plot No. 25-27, Survey No. 366 Premier Industrial Estate Kachigam, Daman – 396 210 (UT) India
Active Pharmaceutical Ingredient(s) (API)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, Drugs for treatment of tuberculosis (J04AK01)
Therapeutic indication	[TB159 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB159 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*. [TB159 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 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)
Pyrazinamide is described in Ph. Int., Ph. Eur. and USP.

60 months of real-time data (25 ± 2ºC/60 ± 5% RH) were submitted for three pyrazinamide batches. All results remained within specifications. The submitted stability studies support a three (3) year retest period on condition that pyrazinamide is stored in the original containers and at a temperature not exceeding 25ºC.

A certificate of suitability was submitted with a Declaration of Access from the API manufacturer to prove that the API from the approved source complies with the requirements of the Ph. Eur., and the holder has declared the absence of material of human or animal origin. Approved specifications control the quality of API (synthesis and process impurities).

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

Other ingredients
All other ingredients in the pharmaceutical product meet pharmacopoeial requirements. Statements have also been provided from the suppliers of each excipient stating that all ingredients are of non-animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
The applicant has presented a compatibility study (API with individual excipients in 1:1 ratio) at 55ºC for 2 weeks, at 40ºC/75%RH and 25ºC/69%RH for 4 weeks with the conclusion that pyrazinamide is compatible with the used excipients.
A dissolution profile for a production-scale batch demonstrated that more than 85% of pyrazinamide dissolved within 15 minutes.
The manufacturing process for [TB159 trade name] is a conventional wet granulation followed by compression and packaging.
In-process controls include monitoring of the unit operations at acceptable intervals.
The finished product is tested according to the BP monograph plus a validated in-house HPLC test for related substances.
A trend data along with graphical presentation were provided for 10 batches of [TB159 trade name] manufactured during the past two years. The presented data indicate that manufacturing process is robust enough to yield consistently the product meeting acceptance criteria.

Stability testing
Since stability data on [TB159 trade name] were submitted on one production batch and two smaller batches, packed in LDPE bags (1000 tablets) further packed in HDPE containers(850 mL) sealed with aluminium taggers, the holder of the prequalification letter committed to put additional two (2) production-scale batches on long-term stability testing. Any out-of-specification (OoS) results or significant change during the commitment study should immediately be reported to WHO.

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 – 1 x Pyrazinamide 500 mg tablet Batch no. PI501 (Macleods Pharmaceutical Ltd., India)
Treatment R:	Reference – 1 x Rolab-Pyrazinamide 500 tablet Batch no. 135097 (Novartis, South Africa)

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 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 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) arrithm.mean (± SD)	Reference (R) arrithm. mean (± SD)	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

*geometric mean

The results of the study show that the pre-set 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, South Africa).

The product intended to be marketed is the pyrazinamide 400 mg tablet (Macleods Pharmaceutical Ltd., India). A biowaiver for the lower strength can be considered if the preparation meets the following criteria:

- the qualitative composition between the strengths is essentially the same;
- the ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
- an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
- in case of systemic availability pharmacokinetics have been shown to be linear over the therapeutic dose range.

The above-mentioned criteria have been met for the dose proportional 400 mg pyrazinamide tablets (compared to the 500 mg pyrazinamide tablets). In addition, dissolution test at a pH of 1.2, 4.5 and 6.8 have shown comparable dissolution of the 400 and 500 mg tablets. Therefore, a biowaiver can be granted for the 400 mg pyrazinamide tablets.

4. Summary of product safety and efficacy

[TB159 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, [TB159 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Rolab-Pyrazinamide 500 mg tablets (Novartis, South Africa) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB159 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 [TB159 trade name] is used in accordance with the SmPC.

Bioequivalence
[TB159 trade name] has been shown to be bioequivalent with Rolab-Pyrazinamide 500 mg tablets (Novartis, South Africa).

Efficacy and Safety
Regarding clinical efficacy and safety, [TB159 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 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 [TB159 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 to include [TB159 trade name], manufactured at Macleods Pharmaceutical Limited, Unit II, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396 210 (UT), India in the list of prequalified medicinal products.