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:	[TB223 trade name][1]
Manufacturer of Prequalified Product:	Micro Labs Limited 15/A, II Phase, Kumbalgodu Industrial Area Bangalore - 560074 Karnataka India
Active Pharmaceutical Ingredients (APIs):	Ethambutol hydrochloride, isoniazid, pyrazinamide and rifampicin
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02).
Therapeutic indication:	[TB223 trade name] is indicated for the e initial treatment of tuberculosis, caused by *Mycobacterium tuberculosis* in adults and children weighing more than 20kg.

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

1. Introduction

[TB223 trade name] is indicated for the intensive phase treatment of tuberculosis, caused by Mycobacterium tuberculosis in adults and children weighing more than 20kg.

[TB223 trade name] should be initiated by a healthcare 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 Ingredients (APIs)

Based on scientific principles the WHO Prequalification Team – Medicines has identified isoniazid (up to 300 mg oral dose), pyrazinamide (up to 500 mg oral dose) and ethambutol hydrochloride (up to 400 mg oral dose) as BCS class 3 APIs. These APIS are thus regarded highly soluble in aqueous medium over the pH range 1.0 – 6.8.

Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol hydrochloride 150mg/75mg/400mg/275mg film-coatedTablets, are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

With respect to rifampicin particle size distribution (PSD) was considered to be critical quality parameter for performance of the product and justified PSD limits are included in the FPP manufacturer's API specifications.

Other ingredients

Other ingredients used in the core tablet formulation include ethylcellulose, microcrystalline cellulose, crospovidone, povidone, sodium ascorbate and magnesium stearate. The film-coat contains hydroxypropyl methylcellulose / hypromellose, polyethylene glycol, titanium dioxide, talc, Lake Indigo Carmine / FD&C Blue #2, Lake Carmoisine. TSE / BSE free attestations have been provided for all the excipients. Magnesium stearate is of vegetable origin. The colorants comply with foodstuff regulations of the USFDA and EU.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 150 mg rifampicin, 75mg isoniazid, 400mg pyrazinamide and 275mg ethambutol hydrochloride. The multisource product is a pinkish-violet coloured, caplet shaped, biconvex, film coated tablet plain on both the sides. The tablets are packaged in Al-Al strips or in HDPE bottles. The objective of the development programme was to obtain a stable, immediate-release FDC tablet that is bioequivalent to the comparator products listed on the WHO prequalification website. All the excipients used in formulation of the dosage form are well known and widely used as pharmaceutical excipients in oral solid formulations

and comply with the relevant pharmacopoeial monographs. No evidence of incompatibility were found during API-excipient compatibility studies.

According to literature, rifampicin is not only prone to hydrolysis and oxidation, but it can also react with isoniazid to form a hydrazone. This hydrazone is described in the Ph.Int. monograph of rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets. The manufacture involves two separate non-aqueous granulation processes, one for ethambutol hydrochloride and the other for isoniazid and pyrazinamide. The dried granules are blended with rifampicin (compacted form) and compressed. Satisfactory in-process controls have been established.

Specifications
The finished product specifications are pharmacopoeial based and include tests for appearance, identification (HPLC, TLC), average weight, uniformity of weight, loss on drying, disintegration time, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbial limits. The test methods have been satisfactorily validated.

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 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The data showed a notable increase in rifampicin related degradation products, though remaining within agreed limits, at all storage conditions in both pack types. 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, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of two tablets of FDC containing isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, ethambutol 275 mg of Micro Labs Ltd., with Rifinah® 300 (rifampicin and isoniazid) tablet of Gruppo Lepetit SpA, Myambutol® 400 mg (ethambutol) tablet of Riemser Arzneimittel AG and two tablets of Pyrazinamid (Lederl) 500 mg of Riemser Arzneimittel AG, in normal, healthy, adult, male and female human subjects under fasting condition (study no. ARL/09/439).

The objective of the study was to compare the bioavailability of the stated ethambutol/ isoniazid/pyrazinamide/rifampicin 275mg/75mg/400mg/150mg FDC tablet manufactured by/for Micro Labs Ltd., India (test drug) with the reference formulations Myambutol® (Riemser Arzneimittel AG), Rifinah® (Gruppo Lepetit SpA) and Pyrazinamid Lederle 500 mg (Riemser Arzneimittel AG) 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 two treatments in a randomized fashion

Treatment T: *Test*
2 tablets ethambutol HCl/isoniazid/pyrazinamide/rifampicin 275mg/75mg/400mg/150mg
(ethambutol 550 mg + isoniazid 150mg + pyrazinamide 800 mg + rifampicin 300 mg)
Batch no. RIPEK9003

Treatment R: *References*
- 1 tablet Myambutol® (ethambutol 400 mg) Batch no. 709470
- 1 tablet Rifinah® (isoniazid 150 mg + rifampicin 300 mg) Batch no. A8341
- 2 tablets pyrazinamide 500 mg (pyrazinamide 1000 mg) Batch no. 803100

A 13-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 28 samples within 60 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for ethambutol, isoniazid, pyrazinamide and rifampicin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 51 ng/ml for ethambutol, 100 ng/ml for isoniazid, 1003 ng/ml for pyrazinamide and 100 ng/ml for rifampicin.

The study was performed with 62 participants. Data generated from a total of 60 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ethambutol (dose normalised for AUC and Cmax), isoniazid, pyrazinamide (dose normalised for AUC and Cmax) and rifampicin as well as statistical results are summarised in the following tables:

Rifampicin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	2.09 ± 0.94	2.63 ± 1.15	-	-
Cmax (ng/mL)	6208 ± 1613 (6011)	6075 ± 1727 (5803)	103.6	98.6-108.9
AUC0-t (ng.h/mL)	37168 ± 12853 (35305)	37630 ± 13321 (35292)	100.0	95.3-105.0
AUC0-inf (ng.h/mL)	40838 ± 12958 (39102)	41829 ± 13554 (39554)	98.9	94.5-103.4

* geometric mean

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	1.11 ± 0.83	1.11 ± 0.87	-	-
Cmax (ng/mL)	4036 ± 1640 (3686)	3981 ± 1752 (3603)	102.3	92.3 113.3
AUC_{0-t} (ng.h/mL)	14385 ± 6892 (12569)	14353 ± 6847 (12513)	100.4	97.8-103.1

$AUC_{0\text{-}inf}$ (µg.h/mL)	15694 ± 7479 (13689)	15657 ± 7467 (13629)	100.4	98.1-102.8

* geometric mean

Pyrazinamide

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	1.29 ± 0.83	1.48 ± 0.92	-	-
Cmax (ng/mL)	6208 ± 1613 (6011)	25645 ± 5782 (25047)	113.2	107.7-118.9
AUC0-t (ng.h/mL)	37168 ± 12853 (35305)	289478 ± 72027 (280763)	100.0	97.0-103.1
AUC0-inf (ng.h/mL)	40838 ± 12958 (39102)	336633 ± 70675 (329100)	101.6	98.8-104.4

* geometric mean

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	3.07 ± 1.15	3.45 ± 1.17	-	-
Cmax (ng/mL)	1705 ± 997 (1463)	1488 ± 765 (1343)	103.6	98.6-108.9
AUC0-t (ng.h/mL)	7832 ± 2183 (7496)	7780 ± 2029 (7488)	100.0	95.3-105.0
$AUC_{0\text{-}inf}$ (ng.h/mL)	8616 ± 2299 (8286)	8618 ± 2107 (8343)	98.9	94.5-103.4

* geometric mean

Conclusion

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding ethambutol, isoniazid, pyrazinamide and rifampicin. Accordingly, the test FDC tablet ethambutol/isoniazid/pyrazinamide/rifampicin 275mg/75mg/400mg/150mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the references Myambutol® (Riemser Arzneimittel AG), Rifinah® (Gruppo Lepetit SpA) and Pyrazinamid Lederle 500 mg (Riemser Arzneimittel AG).

4. Summary of Product Safety and Efficacy

[TB223 trade name] has been shown to conform to the samerelevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability, [TB223 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference products pharmaceutically and therapeutically equivalent to the reference products, Myambutol® (Riemser Arzneimittel AG), Rifinah® (Gruppo Lepetit SpA) and

Pyrazinamid Lederle 500 mg (Riemser Arzneimittel AG).
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 account. Reference is made 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 clinical performance of the product 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 [TB223 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB223 trade name] has shown to be bioequivalent with Tablets has shown to be bioequivalent with Myambutol® (Riemser Arzneimittel AG), Ri finah ® (Gruppo Lepetit SpA) and Pyrazinamid Lederle 500 mg (Riemser Arzneimittel AG).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB223 trade name] are considered effective and safe to use when the guidance and restrictions 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 that the benefit risk profile of [TB223 trade name] was acceptable for the following indication: **"initial treatment phase of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children weighing more than 20kg"** and has advised that quality, efficacy and safety of [TB223 trade name] allow inclusion of [TB223 trade name], manufactured at Micro Labs Limited, 15/A, II Phase, Kumbalgodu Industrial Area, Bangalore 560074, India, in the list of prequalified medicinal products.