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:	[TB356 trade name][*]
Manufacturer of Prequalified Product:	Micro Labs Limited, Unit 3, 92 Sipcot Industrial Complex Hosur 635 126, Tamil Nadu, India.
Active Pharmaceutical Ingredient (API):	Levofloxacin
Pharmaco-therapeutic group (ATC Code):	Antibacterial for systemic use, fluoroquinolone, (J01MA12)
Therapeutic indication:	[TB356 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB356 trade name] is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

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

1. Introduction

[TB356 trade name]is indicated in combination with other antituberculosis agents for the treatment of tuberculosis in children below 15 years of age.

[TB356 trade name] should be prescribed by a physician experienced in the management of tuberculosis.

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)

Levofloxacin is the S-enantiomer of the racemic ofloxacin. The pharmaceutical form is levofloxacin hemihydrate, (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.
Based on scientific principles WHO PQTm has identified levofloxacin (up to 750 mg oral dose) as a BCS class 1 API. Levofloxacin is thus highly soluble according to the BCS.
The API specifications include tests for appearance, solubility, identification (IR, HPLC), specific optical rotation, water content, sulfated ash, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC), bulk density (tapped and untapped) 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.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, hypromellose, colloidal anhydrous silica, magnesium stearate and sucralose, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary pineapple flavour which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications.TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a light -yellow to yellow-coloured, circular, flat faced bevelled edge, uncoated tablet with deep break line on one face and shallow convex with 'LDT' debossing on other face. 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 Alu-PVC/PE/PVdC blister packs.

The objective of the development activities was to obtain a formulation of the dispersible tablets that would be bioequivalent to the WHO recommended comparator product, Tavanic® 500 mg film-coated tablets. The selection of excipients in the formulation of the dispersible tablets was based on API-excipient compatibility studies, similarity with the comparator product and the manufacturer's previous experience with similar dosage forms which have been prequalified. Sucralose and pineapple flavour are used as sweetener and flavouring agent, respectively, in the dispersible tablets. The dispersible tablets are manufactured using wet granulation method. Various studies were performed to optimize the concentration of the functional excipients and process parameters to obtain a product of desired characteristics, including acceptability and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for appearance, identification (IR, HPLC), average

mass, tablet dimensions, disintegration time limit (3 min), resistance to crushing, friability, water content (by KF), fineness of dispersion, uniformity of dosage units (by mass variation), dissolution (UV detection), assay (HPLC), related substances (HPLC), subdivision of tablets and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, showing no out -of-specification results for all the parameters tested. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.
The reconstituted preparation (tablets dispersed in water) should be consumed within 10 minutes.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

An open-label, randomized, balanced, single-dose, two-treatment, two-period, two-sequence, crossover oral bioequivalence study of 5 tablets of Levofloxacin dispersible tablets 100 mg manufactured by Micro Labs Limited., India and 1 tablet of Tavanic®500 mg film tablet levofloxacin, manufactured by Sanofi Winthrop Industrie 56, route de Choisy-au-Bac, F-60205 Compiegne in healthy, adult, human subjects under fasting conditions (study no. 056-17).

The objective of the study was to compare the bioavailability of the stated Levofloxacin 100 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Tavanic® (Sanofi Winthrop) 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 – 5 dispersible tablets Levofloxacin 100 mg (levofloxacin 500 mg) Batch no. LFAHH0002.
Treatment R:	Reference – 1 tablet Tavanic® (levofloxacin 500 mg) Batch no. 6EH3A/A.

The test tablet was dispersed in 50 mL water before intake. The reference tablet was taken with 240 ml water. A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 36 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 levofloxacin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for levofloxacin.

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 levofloxacin as well as statistical results are summarised in the following table:

Levofloxacin

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 (ANOVA log)
t_{max} (h)	0.75 (0.33 – 2.75)	1.0 (0.5 – 3.0)	-	-
C_{max} (µg/mL)	6.07 ± 1.79 (6.37)	6.66 ± 2.10 (5.84)	91.7	84.1 – 99.9

AUC_{0-t} (µg·h/mL)	41.1 ± 6.4 (42.1)	42.9 ± 7.7 (40.6)	96.5	92.9 – 100.2
AUC_{0-inf} (µg·h/mL)	42.7 ± 6.5 (43.7)	44.5 ± 7.9 (42.2)	96.6	93.1 – 100.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding levofloxacin. Accordingly, the test Levofloxacin 100 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tavanic® (Sanofi Winthrop).

4. Summary of Product Safety and Efficacy

[TB356 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, [TB356 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator product Tavanic®500 mg tablets for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated 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 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 [TB356 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB356 trade name] has shown to be bioequivalent with Tavanic® (Levofloxacin 500 mg tablets), Sanofi Winthrop Industrie, France.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB356 trade name] 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 [TB356 trade name] was acceptable for the following indication**: "as a second-line antimycobacterial drug in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*"** and has advised that the quality, efficacy and safety of [TB356 trade name] allow inclusion of [TB356 trade name], manufactured at Micro Labs Ltd, Unit 3, 92 Sipcot Industrial Complex, Hosur 635 126, Tamil Nadu, India in the list of prequalified medicinal products.