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	[TB349 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited (Unit – 03) 92, Sipcot Industrial Complex Hosur – 635126 Tamil Nadu India
Active Pharmaceutical Ingredient(s) (API)	Moxifloxacin (as hydrochloride)
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, Fluoroquinolones (J01 MA14)
Therapeutic indication	[TB349 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in children weighing between 5 kg and 30 kg.

1. Introduction

[TB349 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in children weighing between 5 kg and 30 kg.

[TB349 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.

[TB349 trade name] should be initiated by a health care provider 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)

Based on scientific principles the WHO Prequalification Team – Medicines has identified moxifloxacin (as hydrochloride) up to 400 mg oral dose as a BCS class 1 API, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble.

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control quality of the API. Additional user requirements include particle size distribution and bulk density.

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 microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, pineapple flavour and sucralose, all except pineapple flavour being pharmacopoeial controlled. None of the excipients are derived from animal origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a light yellow to yellow-coloured, circular, flat-faced, bevel-edged, uncoated tablet with a deep score-line (snap tab) on one face and shallow convex with "M" above "100" debossed on the other face. The tablets are presented in white opaque PVC/PE/PVdC-Alu blisters and Alu-Alu strip packs.

The development of the final composition of multisource product has been described. The aim was to develop tablets which would be suitable for paediatric use and bioequivalent to the comparator product, Avelox® 400 mg tablets. The comparator product was characterized in support of the development and for defining a quality target product profile. The excipients selected are generally used in tablet formulations. The major excipients are qualitatively similar to that of the comparator product, with additional ones required for the dispersible formulation. A commercially available pineapple flavour and sucralose are added to serve as flavour and sweetener respectively in this paediatric formulation. For manufacture of [TB349 trade name] wet granulation process was used. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include appropriate tests for appearance, identification (IR and HPLC), average mass, tablet dimensions, disintegration time, resistance to crushing, friability, water content (KF), fineness of dispersion, uniformity of dosage units (by mass variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) 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 stable at both long term and accelerated storage conditions. The product should be protected from light and moisture. 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 2017 according to internationally accepted guidelines.

An open-label, randomized, balanced, single-dose, two-treatment, two-period, two-sequence, crossover oral bioequivalence study of 4 tablets of [TB349 trade name] manufactured by Micro Labs Limited., India and 1 tablet of Avelox® (moxifloxacin hydrochloride) equivalent to 400 mg moxifloxacin tablets, Avelox is a registered trademark of Bayer Aktiengesellschaft and is used under license by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse station NJ 08889 USA in 32 healthy, adult, human subjects under fasting conditions (study no. 096-16-WHO).

The objective of the study was to compare the bioavailability of the stated [TB349 trade name] manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Avelox® (Bayer Healthcare) 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 – 4 [TB349 trade name] (moxifloxacin 400 mg) Batch no. MDAEH0001.
Treatment R: Reference – 1 tablet Avelox® (moxifloxacin 400 mg) Batch no. BXH1P61.

A 6 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 48 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 moxifloxacin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for moxifloxacin.

The study was performed with 32 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Moxifloxacin

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)#	0.92 (0.33 – 2.67)	0.92 (0.33 – 3.0)	–	–
C_{max} (µg/mL)	3.22 ± 0.74 (3.14)	3.33 ± 0.73 (3.25)	96.5	89.5 – 104.0
AUC_{0-t} (µg·h/mL)	28.9 ± 4.8 (28.5)	29.5 ± 5.4 (29.0)	98.3	96.4 – 100.3
AUC_{0-inf} (µg·h/mL)	30.8 ± 5.2 (30.3)	31.3 ± 5.8 (30.8)	98.5	96.7 – 100.3

median (range)

The results of the study show that preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding moxifloxacin. Accordingly, the test [TB349 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Avelox® (Bayer Healthcare).

4. Summary of product safety and efficacy

[TB349 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, [TB349 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product 400 mg moxifloxacin tablets, Avelox® (Bayer Aktiengesellschaft) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB349 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 [TB349 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB349 trade name] has been shown to be bioequivalent with Avelox® (Bayer Aktiengesellschaft).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB349 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 [TB349 trade name] was acceptable for the following indication: 'in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*" in children weighing between 5 kg and 30 kg', and would allow inclusion of [TB349 trade name], manufactured at Micro Labs Limited, (Unit-03) 92, Sipcot Industrial Complex, Hosur-635126, Tamil Nadu, India, in the list of prequalified medicinal products.