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	[TB263 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited Unit: – 03 92, Sipcot Industrial Complex Hosur – 635126 Tamilnadu India
Active Pharmaceutical Ingredient(s) (API)	Moxifloxacin
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication	[TB263 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB263 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis.

[TB263 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.

[TB263 trade name] should be prescribed by a health care 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 Ingredient (API)

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

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

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.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol, iron oxide yellow and iron oxide red. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink coloured, capsule shaped, biconvex, bevelled edge, film coated tablet marked with "MF" on one side and plain on other side. The tablets are presented in PVC/PE/PVdC-Al blisters, cold formable Al–Al blisters and HDPE bottles with polypropylene screw caps.

The development of the final composition of multisource product has been described. The aim was to develop tablets which would be 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 for the core tablets are similar to those of the comparator product. For manufacture of the core tablets a conventional wet granulation process was selected. 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 (HPLC and UV), average mass, uniformity of dosage units (by mass variation), disintegration time, resistance to crushing, dissolution (HPLC), water content (KF), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30ºC/75%RH (zone IVb) as long-term storage condition and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend in all packaging configurations. The product should be protected from light. 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 2012 according to internationally accepted guidelines:

Study title: A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover bioequivalence study of Moxifloxacin Tablets 400 mg of Micro Labs Ltd., India and Avelox® 400 mg film-coated tablet moxifloxacin, of Bayer B.V., Energieweg 1, 3641. RT Mijdrecht, in normal, healthy, adult, human subjects under fasting conditions (study no. NCS-04212-CS).

The objective of the study was to compare the bioavailability of the stated Moxifloxacin 400 mg tablets manufactured for/by Micro Labs Ltd., India (test drug) with the reference formulation Avelox® (Bayer B.V.) 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 treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Moxifloxacin 400 mg (moxifloxacin 400 mg) Batch no. MXBHH0003
Treatment R:	Reference – 1 tablet Avelox® (moxifloxacin 400 mg) Batch no. BXFPHE1

A 6-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 60 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 51 ng/ml for moxifloxacin.

The study was performed with 32 participants; data generated from a total of 30 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)	1.71 ± 1.21	1.96 ± 1.16	-	-
C_{max} (µg/mL)	2.81 ± 0.66 (2.74)	2.62 ± 0.71 (2.55)	107.2	97.9 – 117.3
AUC_{0-t} (µg.h/mL)	31.3 ± 4.9 (30.9)	31.1 ± 5.2 (30.8)	100.5	98.3 – 102.7
AUC_{0-inf} (µg.h/mL)	33.2 ± 5.7 (32.7)	32.8 ± 5.7 (32.4)	101.0	98.8 – 103.2

Conclusion

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 tablet Moxifloxacin 400 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Avelox® (Bayer B.V.).

4. Summary of product safety and efficacy

[TB263 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, [TB263 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Avelox® (Bayer B.V.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB263 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 [TB263 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB263 trade name] has been shown to be bioequivalent with Avelox® 400 mg tablets (Bayer B.V.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB263 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 [TB263 trade name] was acceptable for the following indication: 'in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis', and would allow inclusion of [TB263 trade name], manufactured at Micro Labs Limited Unit: – 03, 92, Sipcot Industrial Complex, Hosur – 635126, Tamilnadu, India in the list of prequalified medicinal products.