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	[TB341 trade name][*]
Manufacturer of Prequalified Product	MSN Laboratories Private Limited Formulation Division Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal) Rangareddy District Telangana – 509228 India
Active Pharmaceutical Ingredient (API)	Moxifloxacin (as hydrochloride)
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication	[TB341 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB341 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB341 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.

[TB341 trade name] should be prescribed by a physician 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 400 mg oral dose as a BCS class 1 API, eligible for BCS-based biowaiver applications. The API is thus regarded highly soluble in terms of the BCS.

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.

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 core tablet formulation include lactose monohydrate, povidone, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. BSE/TSE compliance declarations were provided for the excipients. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, polyethylene glycol and iron oxide red.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a dull red coloured, capsule shaped, bevelled, film coated tablet, debossed with "M400" on one side and a break line on the other side. The tablets are presented in clear PVC/PVDC-Al blisters and in white opaque HDPE bottles.

The multisource product was developed as an immediate release; solid oral tablet dosage form that would be bioequivalent to the WHO recommended comparator product, Avelox® 400 mg tablets. The excipients selected for the core tablets are conventional pharmaceutical ingredients, included in the formulation at suitable levels for recognised purposes. The compatibility of the excipients with the API was demonstrated by API-excipient stress studies.

Due to poor flow properties of the API, an aqueous wet granulation processes was selected for manufacture of the core tablets. 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 description, identification of the API (HPLC, IR) and colouring agents, average tablet mass, uniformity of dosage units (by mass variation), disintegration time, water content (KF), breakability, dissolution (UV detection), assay (HPLC), related substances (HPLC) and microbial limits. The test procedures have been adequately described and suitably validated.

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 condition 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. 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 2016 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Moxifloxacin hydrochloride 400 mg tablets of MSN Laboratories Private Limited, India comparing with that of Avelox® (moxifloxacin hydrochloride) 400 mg tablets of Merck Sharp & Dohme Corp., a subsidiary of Merck & CO., INC, USA in healthy, adult, human subjects under fasting conditions (study no. 661/16).

The objective of the study was to compare the bioavailability of [TB341 trade name], manufactured by/for MSN Laboratories Private Limited, India (test drug) with the reference formulation Avelox® (Merck Sharp & Dohme Corp.) and to assess bioequivalence. The comparison was performed as a

single centre, open label, randomised, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T: Test – 1 tablet [TB341 trade name] (moxifloxacin (as hydrochloride) 400 mg) Batch no. DT1502001A.

Treatment R: Reference – 1 tablet Avelox® (moxifloxacin (as hydrochloride) 400 mg) Batch no. BXH5S71A.

A 9 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 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 20 ng/mL for moxifloxacin.

The study was performed with 28 participants; data generated from a total of 27 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)	1.15 ± 0.92	1.04 ± 0.89	–	–
C_{max} (ng/mL)	3089 ± 828 (2967)	2975 ± 800 (2878)	103.1	95.2 – 111.7
AUC_{0-t} (ng·h/mL)	32872 ± 5057 (32459)	32689 ± 4645 (32390)	100.2	98.7 – 101.8
AUC_{0-inf} (ng·h/mL)	33794 ± 5272 (33353)	33545 ± 4944 (33217)	100.4	98.8 – 102.1

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding rifampicin. Accordingly, the test [TB341 trade name] tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Avelox® 400 mg tablet (Merck Sharp & Dohme Corp.).

4. Summary of product safety and efficacy

[TB341 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, [TB341 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Avelox® 400 mg tablets for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB341 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 [TB341 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB341 trade name] has shown to be bioequivalent with Avelox® 400 mg tablets (Merck Sharp & Dohme Corp., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB341 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 [TB341 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 [TB341 trade name], manufactured at MSN Laboratories Private Limited - Formulation Division, Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana-509228, India, in the list of prequalified medicinal products.