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	[TB342 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceutical Limited Unit-VI, Production Block N2, Village Theda, P.O. Lodhimajra,Tehsil Baddi, District Solan, Himachal Pradesh-174101 India
Active Pharmaceutical Ingredient (API)	Moxifloxacin (as hydrochloride)
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication	[TB342 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

[TB342 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.
[TB342 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.
[TB342 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 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. Additional user requirements include bulk density, particle size distribution and polymorphism.

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

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 ethylcellulose, methacrylic acid copolymer, triethyl citrate, mannitol, microcrystalline cellulose, sucralose, sodium chloride, crospovidone, aspartame, magnesium stearate, lemon flavour and peppermint flavour. All the non-flavour excipients used in the manufacture of the finished pharmaceutical product are well known pharmaceutical excipients with established uses in tablet formulations. 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 mottled yellow colour, capsule-shaped, biconvex, uncoated dispersible tablet, debossed with "I 75" on one side and with a break-line on the other side. The tablets are presented in Alu-Alu blister cards made of aluminium foil and cold form laminate.

The objective of formulation and development was to develop a stable and robust formulation which is bioequivalent to the WHO recommended comparator product, Avelox® 400 mg tablets. The comparator product was characterized to define a quality target product profile. Commercially available lemon and peppermint flavours are added in this paediatric formulation.

Due to the poor flow properties of the drug substance and to avoid multiple granulations, top spray granulation process was selected to manufacture the drug product for ease of processing. The formulation and process parameters were optimised, in order to have similar dissolution profiles with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), average weight, friability, hardness, disintegration time, loss on drying, fineness of dispersion, uniformity of dosage units (by content uniformity), dissolution (UV detection), related substances (HPLC), residual solvent, assay (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 condition 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 2016 according to internationally accepted guidelines.
Four tablets as single oral dose fasting in vivo bioequivalence study of Moxifloxacin hydrochloride dispersible tablets 100 mg (Macleods Pharmaceuticals Ltd., India) with Avelox® (moxifloxacin

hydrochloride) film coated tablets 400 mg (Bayer plc, UK) in healthy, adult, human subjects (study no. BEQ-2055-MOXI-2016).

The objective of the study was to compare the bioavailability of the stated moxifloxacin (as hydrochloride) 100 mg dispersible tablets manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Avelox® (Bayer plc.) 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 dispersible tablets moxifloxacin hydrochloride 100 mg (moxifloxacin 400 mg)
Batch no. BMC5503B.

Treatment R: Reference – 1 tablet Avelox®
(moxifloxacin 400 mg)
Batch no. BXGTVX1.

The test formulation (4 × 100 mg tablets) was dispersed in 50 mL of drinking water before dosing. A 4-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 48 hours 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 analysed 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 24 participants. Data generated from a total of 22 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.16 ± 0.74	1.47 ± 0.88	-	-
C_{max} (ng/mL)	2982 ± 777 (2893)	2872 ± 725 (2791)	103.6	94.6 – 113.6
AUC_{0-t} (ng·h/mL)	30585 ± 4790 (30232)	31263 ± 5570 (30799)	98.2	96.5 – 99.9
AUC_{0-inf} (ng·h/mL)	32140 ± 5272 --	32872 ± 5964 --	-	-

* geometric mean

The results of the study show that pre-set acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding moxifloxacin. Accordingly, the test moxifloxacin (as hydrochloride) 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 Avelox® (Bayer plc.).

4. Summary of product safety and efficacy

[TB342 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, [TB342 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Avelox® (Bayer plc.) for which benefits have been

proven in terms of clinical efficacy. The clinical safety of [TB342 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 [TB342 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB342 trade name] has been shown to be bioequivalent with Avelox® (Bayer plc.)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB342 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 [TB342 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 [TB342 trade name], manufactured at Macleods Pharmaceutical Limited, Unit-VI, Production Block N2, Village Theda, P.O. Lodhimajra, Tehsil Baddi, District Solan, Himachal Pradesh-174101, India, in the list of prequalified medicinal products.