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:	[TB230 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Unit II, Plot No. 25-27 Survey No. 366, Premier Industrial Estate Kachigam, Daman (U.T.) India Telephone: + 91 0260 2244337 Fax: + 91 0260 2241565
Active Pharmaceutical Ingredient (API):	Moxifloxacin
Pharmaco-therapeutic group (ATC Code):	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication:	[TB230 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

[TB230 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB230 trade name] should be prescribed by a physician experienced in the management of tuberculosis infection.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredient (API)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified moxifloxacin (up to 400mg 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 (tapped and untapped).

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 croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Magnesium stearate is of vegetable origin. The film coat contains hydroxypropyl methylcellulose, iron oxide red, polyethylene glycol, purified talc and titanium dioxide.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture
Moxifloxacin (as hydrochloride) 400mg Tablets are brick-red coloured, capsule shaped, biconvex, film-coated tablets, plain on both the sides. The tablets are packaged in Alu-Alu cold form blisters and Alu-Alu strips.

The development of the final composition of Moxifloxacin (as hydrochloride) 400mg Tablets has been described. The aim was to develop tablets, which would be bioequivalent to the comparator product, Avelox® 400 mg film-coated tablets. The selection of excipients in the formulation was based on their compatibility with moxifloxacin hydrochloride and their suitability to achieve the desired characteristics of the tablets.

For manufacture of the core tablets a conventional wet granulation process was selected. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data demonstrated the consistency of the process.

Product specification
The finished product specifications are regarded adequate for ensuring consistent quality of this FPP and include tests for description, identification of the API (HPLC, UV and chloride counter ion) and colorants, average weight, uniformity of dosage units (by mass variation), disintegration time, loss on drying, dissolution (UV detection), related substances (HPLC), assay (HPLC)and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/70%RH as long-term storage condition and for six months at accelerated conditions for tablets in Alu-Alu cold form blister packs and Alu-Alu strip packs. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2010 according to internationally accepted guidelines.

Bioequivalence study of single dose Moximac (moxifloxacin) tablets 400 mg (each film coated tablet contains moxifloxacin hydrochloride equivalent to moxifloxacin 400 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Avelox® (moxifloxacin hydrochloride) tablets 400 mg (each tablet contains moxifloxacin hydrochloride equivalent to 400 mg of moxifloxacin) manufactured by Bayer Health Care, Germany in healthy, adult, human subjects under fasting condition (study no. BEQ-505-MOXI-2010)

The objective of the study was to compare the bioavailability of the stated Moximac 400 mg tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference formulation (Avelox®, Bayer Health Care) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Moximac 400 mg (moxifloxacin 400 mg) Batch no. MX805.
Treatment R:	Reference – 1 tablet Avelox® (moxifloxacin 400 mg) Batch no. 540130X.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 100 ng/ml for moxifloxacin.

The study was performed with 24 participants; data generated from a total of 24 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 tables:

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)	2.30 ± 1.09	1.82 ± 1.35	-	-
C_{max} (µg/ml)	2.123 ± 0.679 (2.039)	2.256 ± 0.835 (2.139)	95.4	85.1 – 106.9
AUC_{0-t} (µg.h/ml)	25.7 ± 6.7 (24.9)	24.6 ± 6.1 (23.9)	103.9	99.5 – 108.6
AUC_{0-inf} (µg.h/ml)	29.4 ± 5.7 (28.9)	28.8 ± 5.7 (28.4)	102.0	99.8 – 104.1

* geometric mean

Conclusions:

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 Moximac 400 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Avelox® (Bayer Health Care).

4. Summary of Product Safety and Efficacy

[TB230 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [TB230 trade name]is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Avelox® 400 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 [TB230 trade name]is used in accordance with the SmPC.

Bioequivalence

[TB230 trade name] has shown to be bioequivalent with Avelox® 400 mg tablets, Bayer, Germany.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB230 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 [TB230 trade name] was acceptable for the following indication: "**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 [TB230 trade name] allow inclusion of Moxifloxacin 400mg tablets, manufactured at Macleods Pharmaceuticals Limited, Unit II, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman (U.T.),India in the list of prequalified medicinal products.