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:	[TB311 trade name][*]
Manufacturer of Prequalified Product:	Getz Pharma (Pvt) Limited 29-30/27, Korangi Industrial Area Karachi-74900 Pakistan
Active Pharmaceutical Ingredient (API):	Moxifloxacin (as hydrochloride)
Pharmaco-therapeutic group (ATC Code):	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication:	[TB311 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB311 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB311 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.

[TB311 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.

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

Moxifloxacin hydrochloride, 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b] pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride is a slightly hygroscopic, light yellow or yellow substance. The API contains two stereogenic carbon centres, with the desired stereochemistry (4aS,7aS) built into one of the starting materials. It is known to exhibit polymorphism. The manufacturing process consistently produces an anhydrous form, which is characterised by XRPD.

The specifications of moxifloxacin hydrochloride are pharmacopoeia based and include tests for appearance, solubility, identification of the API (specific optical rotation, IR) and chloride counter ion, appearance of solution, pH, water (KF), sulfated ash, related substances (HPLC and UFLC-MS), assay (HPLC), sulfate, heavy metals, hydrochloride content, R-isomer content, residual solvents (GC), palladium and nickel content (AAS), particle size and microbial limits.

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 microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate, all being pharmacopoeial controlled. The film coat contains hypromellose, titanium dioxide, macrogol/PEG and ferric oxide. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink, oblong-shaped, film-coated tablet engraved "GETZ" on one side and with a score line on the other side. The score-line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are presented in Alu-Alu blisters cards.

The formulation of Moxifloxacin (as hydrochloride) 400mg Tablets was developed by using common excipients which are compatible with the API. The choice of excipients was made considering the qualitative composition of the WHO recommended comparator product, Avelox® 400 mg tablets. In order to develop the manufacturing process detailed analysis was done on the selection of the granulation process and critical formulation and process attributes. A wet granulation manufacturing method was applied to improve the flow properties of the API. 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, disintegration time, average weight, loss on drying, breaking force, identification of the API (HPLC, UV), assay (HPLC), uniformity of dosage units (by weight variation), dissolution (UV detection), 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 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. 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 Bio-Equivalence

No bioequivalence study has been performed. As moxifloxacin is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Avelox® 400 mg tablet (Bayer Inc.) and the test [TB311 trade name] (Getz Pharma [Pvt] Limited, Pakistan) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 have been shown. Accordingly, the test tablet [TB311 trade name] (Getz Pharma (Pvt) Limited, Pakistan) meets the criteria for a BCS based biowaiver and is therefore, considered bioequivalent to the reference Avelox® 400 mg tablet (Bayer Inc.).

4. Summary of Product Safety and Efficacy

[TB311 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO-recommended comparator product. [TB311 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [TB311 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB311 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB311 trade name] and Avelox® 400 mg tablets (Merck Sharp & Dohme Corp., USA) are bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB311 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 [TB311 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 [TB311 trade name] allow inclusion of [TB311 trade name], manufactured at Getz Pharma (Pvt) Limited, 29-30/27, Korangi Industrial Area,Karachi-74900, Pakistan, in the list of prequalified medicinal products.