This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

**SCIENTIFIC DISCUSSION**

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>Moxifloxacin (as hydrochloride) 400mg Tablets¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of Prequalified Product:</td>
<td>Zhejiang Hisun Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td></td>
<td>E03 Building, 1 Haizheng Avenue</td>
</tr>
<tr>
<td></td>
<td>Jiaojiang District</td>
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<tr>
<td></td>
<td>Taizhou City</td>
</tr>
<tr>
<td></td>
<td>Zhejiang Province 318000</td>
</tr>
<tr>
<td></td>
<td>China</td>
</tr>
<tr>
<td>Active Pharmaceutical Ingredient (API):</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Quinolone antibacterials, Fluoroquinolones</td>
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<tr>
<td></td>
<td>(J01MA14)</td>
</tr>
<tr>
<td>Therapeutic indication:</td>
<td>Moxifloxacin (as hydrochloride) 400mg Tablets</td>
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<tr>
<td></td>
<td>is indicated in combination with other</td>
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<td></td>
<td>antituberculosis agents for the treatment of</td>
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<td></td>
<td>tuberculosis caused by Mycobacterium</td>
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<tr>
<td></td>
<td>tuberculosis.</td>
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</tbody>
</table>

¹ 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

Moxifloxacin (as hydrochloride) 400mg Tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

Moxifloxacin (as hydrochloride) 400mg Tablets is only indicated as a second-line antimycobacterial drug when use of first-line drugs is not appropriate due to resistance or intolerance.

Moxifloxacin (as hydrochloride) 400mg Tablets should be prescribed by a health care provider experienced in the management of tuberculosis infection.

2. Assessment of Quality

The assessment was done according to 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 BCS highly soluble.

Moxifloxacin hydrochloride has been prequalified by WHO according to WHO’s *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of Moxifloxacin (as hydrochloride) 400mg Tablets, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

**Other ingredients**

Other ingredients used in the core tablet formulation include povidone, crospovidone, microcrystalline cellulose and magnesium stearate, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol (part hydrolysed), titanium dioxide, talc, macrogol/PEG, lecithin (soya), iron oxide red, iron oxide black and iron oxide yellow. BSE/TSE compliance declarations were provided.

**Finished pharmaceutical products (FPP)**

**Pharmaceutical development and manufacture**

The multisource product is an oblong, dull red film-coated tablet, plain on both sides. The tablets are presented in PVC/PVdC-Al blister packs.

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, Avalox® 400mg Tablets. The comparator product was characterized in support of the development and for defining a quality target product profile. For formulation development, similar excipients as that of the comparator product were selected and their compatibility with the API demonstrated. 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 description, identification (HPLC and UV), dissolution (HPLC), water content, uniformity of dosage units (by mass variation), related substances (HPLC), assay (HPLC), microbial limits and residual solvent. The test procedures have been adequately validated.

Stability testing
Stability studies have been conducted at 30°C/75%RH 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. Stress studies showed that 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
No bioequivalence study has been performed. As moxifloxacin is selected by the WHO as 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® 400mg Tablets (Bayer Healthcare) and the test Moxifloxacin 400mg Tablets (Zhejiang Hisun Pharmaceutical Co., Ltd, China) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at pH 1.2, 4.5 and 6.8 have been shown. Accordingly, the test Moxifloxacin (as hydrochloride) 400mg Tablets (Zhejiang Hisun Pharmaceutical Co., Ltd., China) meets the criteria for a BCS based biowaiver and is therefore, considered bioequivalent to the reference product Avelox® 400mg Tablets (Bayer Healthcare).

4. Summary of Product Safety and Efficacy
Moxifloxacin (as hydrochloride) 400mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO-recommended comparator product. Moxifloxacin (as hydrochloride) 400mg Tablets 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 Moxifloxacin (as hydrochloride) 400mg Tablets is used in accordance with the SmPC.

Bioequivalence

Moxifloxacin (as hydrochloride) 400mg Tablets fulfilled all criteria for waiving an *in-vivo* bioequivalence study as per relevant WHO guidance. Hence, Moxifloxacin (as hydrochloride) 400mg Tablets and Avelox® 400mg Tablets (Bayer Healthcare) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, Moxifloxacin (as hydrochloride) 400mg Tablets 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 Moxifloxacin (as hydrochloride) 400mg Tablets 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 Moxifloxacin (as hydrochloride) 400mg Tablets allow inclusion of Moxifloxacin (as hydrochloride) 400mg Tablets, manufactured at Zhejiang Hisun Pharmaceutical Co., Ltd., E03 Building, 1 Haizheng Avenue, Jiaojiang District, Taizhou City, Zhejiang Province 318000, China, in the list of prequalified medicinal products.