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	[TB376 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited
Active Pharmaceutical Ingredient(s) (API)	Moxifloxacin (as hydrochloride)
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, fluoroquinolones (J01MA14)
Therapeutic indication	[TB376 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB376 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB376 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.

[TB376 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 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 the 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.

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 commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose,

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

titanium dioxide, macrogol/polyethylene glycol, talc and iron oxide, all controlled by acceptable specifications. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a peach-coloured capsule-shaped, biconvex film-coated tablet having a score line on one side and plain other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in either clear PVC/PVdC-Alu or clear PVC-Alu blister cards.

The objective of formulation development was to obtain a stable and robust formulation which is bioequivalent to the WHO recommended comparator product, Avelox® 400 mg tablets. The core tablet is qualitatively the same as the comparator product with respect to composition. The quality target product profile and critical quality attributes were established. Due to the poor flow properties of the API, wet granulation process was selected to manufacture the tablets. The formulation and process parameters were optimised, in order to have dissolution profiles similar to those of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, average weight, uniformity of weight, identification of the API (HPLC and UV) and colorants, uniformity of dosage units (by mass variation), water content, dissolution (UV detection), assay (HPLC), organic impurities (HPLC), tablet divisibility (by average mass) 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. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are regarded 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 Avalox® 400 mg tablets (Bayer Healthcare) and the test Moxifloxacin 400 mg tablets (Lupin Ltd.) 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 Moxifloxacin 400 mg (Lupin Ltd.) meets the criteria for a BCS-based biowaiver and is therefore considered bioequivalent to the respective reference Avalox® 400 mg tablet (Bayer Healthcare).

4. Summary of product safety and efficacy

[TB376 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB376 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. The clinical safety of [TB376 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 [TB376 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB376 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB376 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 [TB376 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 [TB376 trade name], manufactured at Lupin Limited, Bari Brahmana, Jammu & Kashmir 181 133, India in the list of prequalified medicinal products.