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	[TB381 trade name]*
Manufacturer of Prequalified Product	Remington Pharmaceutical Industries (Pvt) Ltd 18km Multan Road Lahore 53800 Pakistan
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin hemihydrate
Pharmaco-therapeutic group (ATC Code)	Fluoroquinolones (J01MA12)
Therapeutic indication	[TB381 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*. It is also indicated as monotherapy for the prevention of multidrug-resistant tuberculosis in persons at risk.

1. Introduction

[TB381 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

It is also indicated as monotherapy for the prevention of multidrug-resistant tuberculosis in persons at risk.

[TB381 trade name] should be initiated by a healthcare 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)

Levofloxacin hemihydrate has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in 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 [TB381 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components:

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

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 crospovidone, hypromellose, microcrystalline cellulose and sodium stearyl fumarate, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, talc, macrogol, yellow ferric oxide and red ferric oxide. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a light pink coloured, oblong, film coated tablet with a bisect line on both sides. The bisect 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 a clear PVC-aluminium blister card. Each blister card is packed in a mono carton.

The objective of the formulation development strategy was to develop a product with a quality profile similar to that of the WHO recommended comparator product, Tavanic® 250 mg film-coated tablets. The quality target product profile and critical quality attributes were established. The excipients were same as the composition of the WHO recommended comparator product. Wet granulation manufacturing process which was selected was noted to be similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeia based and include tests for description, identification (HPLC and FTIR), optical rotation, water determination (KF), disintegration time, dissolution (UV detection), assay (HPLC), uniformity of dosage unit (weight variation), organic impurities (HPLC) and microbiological examination. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The long-term stability data showed slight increase in the moisture content, though the results remained within the limits. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

No bioequivalence study has been performed. As levofloxacin 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 product Tavanic® 250 mg tablets (Sanofi-Aventis) and the test Levofloxacin 250 mg tablets (Remington Pharm Industries, 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 tablets Levofloxacin 250 mg (Remington Pharm Industries, Pakistan) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the respective reference Tavanic® 250 mg tablets (Sanofi-Aventis).

4. Summary of product safety and efficacy

[TB381 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, [TB381 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tavanic (Sanofi Aventis) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB381 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 [TB381 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB381 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB381 trade name] and Tavanic (Sanofi Aventis) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB381 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 [TB381 trade name] was acceptable for the following indication: 'treatment or prevention of multidrug-resistant tuberculosis due to *Mycobacterium tuberculosis'*, and would allow inclusion of [TB381 trade name], manufactured at Remington Pharmaceutical Industries (Pvt) Ltd, 18km Multan Road, Lahore 53800, Pakistan, in the list of prequalified medicinal products.