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:	[TB355 trade name]*
Manufacturer of Prequalified Product:	Micro Labs Limited Unit 3, 92 Sipcot Industrial Complex Hosur 635 126 Tamil Nadu India.
Active Pharmaceutical Ingredient (API):	Levofloxacin
Pharmaco-therapeutic group (ATC Code):	Antibacterial for systemic use, fluoroquinolone, (J01MA12)
Therapeutic indication:	[TB355 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB355 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.

1. Introduction

[TB355 trade name] in combination with other antituberculosis drugs is indicated in adults and adolescents aged over 14 years and weighing at least 30kg, for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. It should be used only if first-line drugs for treating tuberculosis are inappropriate due to resistance.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

The therapy should be initiated by a health care 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 is the S-enantiomer of the racemic ofloxacin. The pharmaceutical form is levofloxacin hemihydrate, (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

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

Based on scientific principles WHO PQTm has identified levofloxacin (up to 750 mg oral dose) as a BCS class 1 API. Levofloxacin is thus highly soluble according to the BCS.

The API specifications include tests for appearance, solubility, identification (IR, HPLC), specific optical rotation, water content, sulfated ash, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC), bulk density (tapped and untapped) and particle size distribution.

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, crospovidone, hypromellose, croscarmellose sodium and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide yellow and iron oxide red. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a peach coloured, oval shaped, biconvex, film coated tablet, debossed with "750" on one face and plain on the other face. The tablets are presented in either white opaque HDPE bottles secured with child resistant polypropylene cap lined with induction seal or clear transparent PVC-Alu blister packs.

The objective of the development activities was to develop [TB355 trade name] as a scale- up to prequalified Levofloxacin 500 mg and 250 mg Tablets, manufactured by the same manufacturer. The selection of excipients in the formulation was based on API-excipient compatibility studies, similarity with the comparator product, Levaquin®750 mg Tablets and the manufacturer's previous experience with Levofloxacin 500 mg and 250 mg Tablets. The tablets are manufactured using wet granulation method. Various studies were performed to optimize the concentration of the functional excipients and process parameters to obtain a product of desired characteristics and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for appearance, identification (IR, HPLC), average mass, tablet dimensions, disintegration time limit, water content, uniformity of dosage units (by mass variation), dissolution (UV detection), assay (HPLC), related substances (HPLC), residual solvents (GC) and microbial limits.

Stability testing

Stability studies have been conducted at30 °C/75 %RH (zone IVb) as long-term storage condition and for six months at 40 °C/75 %RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, showing no out -of-specification results for all the parameters tested. 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 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 Levaquin® 750 mg tablets (Janssen, US) and the test Levofloxacin 750 mg tablets (Micro Labs. Ltd., India) 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 750 mg (Micro Labs. Ltd., India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the respective reference Levaquin® 750 mg tablets (Janssen, US).

4. Summary of Product Safety and Efficacy

[TB355 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB355 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 [TB355 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB355 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, [TB355 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 [TB355 trade name] was acceptable for the following indication**: "as a second-line antimycobacterial drug 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 [TB355 trade name] allow inclusion of [TB355 trade name], manufactured at Micro Labs Ltd, Unit 3, 92 Sipcot Industrial Complex, Hosur 635 126, Tamil Nadu, India in the list of prequalified medicinal products.