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	[TB237 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited (Unit: ML-03) 92, Sipcot Industrial Complex Hosur – 635126, Tamilnadu, India
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin hemihydrate
Pharmaco-therapeutic group (ATC Code)	Antibacterial for systemic use, fluoroquinolone (J01MA12)
Therapeutic indication	[TB237 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB237 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. [TB237 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.

[TB237 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)

Levofloxacin is the S-enantiomer of the racemic ofloxacin. The pharmaceutical form thereof 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.

Based on scientific principles the WHO Prequalification of Medicines Programme 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 APIMF of levofloxacin hemihydrate has been accepted through WHO's APIMF procedure. It is manufactured in several steps from the commercially available starting materials.

The API specifications include tests for appearance, solubility, identification, absorbance, enantiomeric purity (chiral HPLC; ≤ 0.5%), related substances (HPLC), water content, sulfated ash,

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

heavy metals assay, residual solvents, specific optical rotation, 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 croscarmellose sodium, crospovidone, hydroxypropyl methylcellulose, magnesium stearate and microcrystalline cellulose. The commercially sourced proprietary film-coating mixture contains hypromellose, iron oxide red, iron oxide yellow, macrogol, talc and titanium dioxide. TSE/BSE free declaration has been provided for each excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[TB237 trade name] tablets are peach coloured, capsule shaped, biconvex, film-coated tablets, plain on both the faces. The tablets are presented in clear PVC-aluminium blister cards.

Each tablet contains 256.23 mg of levofloxacin hemihydrate equivalent 250 mg of levofloxacin.

The development was based on evaluation of the physico-chemical properties of comparator product (Levaquin® 250mg film-coated tablets) and the excipients selected from those listed for the comparator product, with the exception of croscarmellose sodium which has been added to facilitate the release of the API from the product. The quality target product profile (QTPP) and critical quality attributes were identified. The wet granulation method was selected over direct compression due to poor flow properties of the powder and its robustness. The QTPP included the average weight, hardness, friability, disintegration and dissolution.

The multisource product showed dissolution profiles similar to that of the comparator product in the BCS media, supporting a biowaiver. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three primary batches demonstrated the consistency of the process.

Specifications

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

Stability testing

Stability studies have been conducted in the packaging intended for marketing of the product at 25°C/60%RH and 30°C/65%RH as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at these conditions, with no significant negative trend. The data support the proposed shelf life and storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

A biowaiver was granted for the [TB237 trade name] manufactured by Micro Labs Limited., India, in accordance to the WHO guideline. In comparison with the comparator Levaquin 250 mg tablets (Janssen Pharms, US), the test product was determined to be qualitatively essentially the same and quantitatively comparable regarding excipients which may affect absorption of levofloxacin.

4. Summary of product safety and efficacy

[TB237 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, [TB237 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Levaquin 250 mg tablets (Janssen Pharms, US), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB237 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 [TB237 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB237 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, [TB237 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 [TB237 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 [TB237 trade name]would allow inclusion of [TB237 trade name], manufactured at Micro Labs Limited (Unit: ML-03) 92, Sipcot Industrial Complex Hosur – 635126 Tamil Nadu, India, in the list of prequalified medicinal products.