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	[TB338 trade name]*
Manufacturer of Prequalified Product	MSN Laboratories Private Limited Formulations Division, Unit-II Survey Nos. 1277, 1319 to 1324 Nandigama (Village & Mandal) Rangareddy District Telangana 509228 India
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin hemihydrate
Pharmaco-therapeutic group (ATC Code)	Antibacterial for systemic use, fluoroquinolone (J01MA12)
Therapeutic indication	[TB338 trade name], in combination with other antituberculosis drugs is indicated for the prevention and treatment of tuberculosis caused by *Mycobacterium tuberculosis*. It should be used only if first-line drugs for treating tuberculosis are inappropriate due to resistance.

1. Introduction

[TB338 trade name], in combination with other antituberculosis drugs is indicated for the prevention and 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 are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC, XRPD), residue on ignition, specific optical rotation, water determination, assay (HPLC), related substances (HPLC), residual solvents (GC), bulk density, untapped density, nickel content (ICP-MS), particle size, clarity of solution, benzene content (GC) and microbiological enumeration.

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, hydroxypropyl methylcellulose and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, propylene glycol, talc and iron oxide red. BSE/TSE compliance declarations were provided. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink-coloured, capsule-shaped, biconvex, film-coated tablet, debossed with 'L' and '2' on one side and plain on the other side. The tablets are packaged in a white opaque HDPE bottle fitted with a white opaque polypropylene child-resistant closure, with wad and induction sealing liner or clear transparent PVC/Alu blisters.

Three tablet strengths, proportionally similar in composition, were developed: 750 mg, 500 mg and 250 mg.

The development of the final composition of the multisource product has been described. The objective was to develop a stable tablet, bioequivalent to the comparator product, Levaquin® film-coated tablets, which is an immediate release solid dosage form for oral administration. The quality target product profile and critical quality attributes were identified. The selection of excipients was based on the comparator product. Due to the poor flow of levofloxacin hemihydrate API, direct compression manufacturing process was found not to be suitable for the finished pharmaceutical product, therefore wet granulation was selected as a method of manufacture of the tablets. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The three strengths showed similar dissolution profiles in the main BCS media, which formed the basis of the biowaivers for the 500 mg and 250 mg strengths.

Specifications

The finished product specifications include tests for description, identification of API (IR, HPLC) and colorants, average weight, uniformity of dosage units (by weight variation), water content (KF), dissolution (UV detection), assay (HPLC) related substances (HPLC), residual solvents and microbiological enumeration. 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 product proved to be quite stable at these conditions, with no apparent negative trend. 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 Levaquin® 250, 500 and 750 mg tablets (Janssen, US) and the respective test Levofloxacin 250, 500 and 750 mg tablets (MSN Laboratories Private Limited, India) 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 tablets Levofloxacin 250, 500 and 750 mg (MSN Laboratories Private Limited, India) meet the criteria for a BCS based biowaiver and are therefore, considered bioequivalent to the respective reference Levaquin® 250, 500 and 750 mg tablets (Janssen, USA).

4. Summary of product safety and efficacy

[TB338 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB338 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. The clinical safety of [TB338 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 [TB338 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB338 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB338 trade name] and Levaquin® 250, 500 and 750 mg tablet (Janssen, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB338 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 [TB338 trade name] was acceptable for the following indication: 'in combination with other antituberculosis drugs for the prevention and treatment of tuberculosis caused by *Mycobacterium tuberculosis'*, and would allow inclusion of [TB338 trade name], manufactured at MSN Laboratories Private Limited, Formulations Division, Unit-II, Survey Numbers 1277, 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana 509228, India in the list of prequalified medicinal products.