

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

<b>Name of the Finished Pharmaceutical Product</b>	[TB339 Trade name]*
<b>Manufacturer of Prequalified Product</b>	MSN Laboratories Private Limited Formulations Division, Unit-II Survey Nos. 1277, 1319 to 1324 Nandigama (Village & Mandal) Rangareddy District Telangana 509228 India
<b>Active Pharmaceutical Ingredient (API)</b>	Levofloxacin hemihydrate
<b>Pharmaco-therapeutic group (ATC Code)</b>	Antibacterial for systemic use, fluoroquinolone (J01MA12)
<b>Therapeutic indication</b>	[TB339 trade name], in combination with other antituberculosis drugs is indicated for the prevention and treatment of tuberculosis caused by <i>Mycobacterium tuberculosis</i> . It should be used only if first-line drugs for treating tuberculosis are inappropriate due to resistance.

### 1. Introduction

[TB339 trade name], in combination with other antituberculosis drugs is indicated for the prevention and treatment of tuberculosis in 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.

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.

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

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 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 tablets with break line on both sides, debossed with 'L' and '5' on one side of the tablet. The tablets are packaged in a white opaque HDPE bottle fitted with 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, breakability test 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, USA) 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) meets 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**

[TB339 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB339 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of [TB339 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 [TB339 trade name] is used in accordance with the SmPC.

#### **Bioequivalence**

[TB339 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB339 trade name] and Levaquin® 250, 500 and 750 mg tablet (Janssen, USA).

#### **Efficacy and Safety**

Regarding clinical efficacy and safety, [TB339 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 [TB339 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 has advised that the quality, efficacy and safety of [TB339 trade name] allow inclusion of [TB339 trade name], manufactured at MSN Laboratories Private Limited, Formulations Division, Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana 509228, India, in the list of prequalified medicinal products.