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	[TB278 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block-N2 Village Theda Post Office Lodhimajra Tehsil Baddi District Solan Himachal Pradesh – 174101 India
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin hemihydrate
Pharmaco-therapeutic group (ATC Code)	Antibacterial for systemic use fluoroquinolone (J01MA12
Therapeutic indication	[TB278 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB278 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

[TB278 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB278 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.

[TB278 trade name] should be prescribed 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-7*H*-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 the WHO PQT-M has identified levofloxacin (up to 750 mg oral dose) as a BCS class 1 API. Levofloxacin is thus highly soluble according to the BCS.

Levofloxacin hemihydrate is manufactured in several steps. The asymmetric centre is introduced via a chiral reagent.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), specific optical rotation, water content (KF), residue on ignition, heavy metals, organic impurities (HPLC), enantiomeric purity (chiral HPLC; ≤ 0.5%), assay (HPLC) and residual solvents.

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 and magnesium stearate. The film-coating contains hypromellose, titanium dioxide, polyethylene glycol, polysorbate, red iron oxide and yellow iron oxide. None of the excipients are of human or animal origin. TSE/BSE free declaration has been provided for each excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[TB278 trade name] are brownish red coloured, capsule shaped, biconvex film coated tablets debossed 'T' & 63 on either side of a deep score line on one side of the tablet and deep score line on the other side. Each tablet contains levofloxacin hemihydrate equivalent to 500 mg of levofloxacin. The score lines are intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in orange coloured PVC-aluminium blisters.

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

The objective of the development activities was to obtain a stable immediate release tablet, bioequivalent to the WHO comparator product Levaquin® tablets. The comparator product was characterised for its physical and chemical properties to define a quality target product profile, including dissolution profiles. The selection of core tablet excipients was based on the qualitative composition of the comparator product, excipient compatibility with the API, and their suitability to achieve the desired tablet characteristics. Since the levofloxacin hemihydrate exhibits poor flow properties, the wet granulation process was selected for manufacture of the core tablets. The critical steps of the manufacturing process were optimized and 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 biowaivers for the lower strengths.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API (HPLC and UV) and colorants, average weight, dissolution (UV detection), uniformity of dosage units (by weight variation), organic impurities (HPLC), assay (HPLC), loss on drying, microbial limits and subdivision of tablets.

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 and storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2009 according to internationally accepted guidelines.

Bioequivalence study of single dose Levofloxacin tablets 750 mg manufactured by Macleods Pharmaceuticals Ltd., India comparing with Levaquin® tablets 750 mg (each tablet contains levofloxacin 750 mg) manufactured by Ortho-McNeil Pharmaceutical, Inc., USA in healthy, adult, human subjects under fasting conditions (study no. BEQ-269-LEVO-2008).

The objective of the study was to compare the bioavailability of the stated Levofloxacin 750 mg tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference formulation (Levaquin®, Ortho-McNeil Pharmaceutical, Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Levofloxacin 750 mg (levofloxacin 750 mg) Batch no. BLG-901.
Treatment R:	Reference – 1 tablet Levaquin® (levofloxacin 750 mg) Batch no. 8MG299

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 48 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for levofloxacin were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 206 ng/ml for levofloxacin.

The study was performed with 32 participants; data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence of levofloxacin.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for levofloxacin as well as statistical results are summarised in the following tables:

Levofloxacin

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.34 ± 0.82	1.44 ± 0.73	–	–
C_{max} µg /mL)	9.16 ± 2.21 (8.90)	8.64 ± 1.67 (8.50)	104.8	97.7 – 112.4
AUC_{0-t} (µg·h/mL)	72.9 ± 11.1 (72.0)	73.1 ± 11.1 (72.3)	99.6	98.0 – 101.2
AUC_{0-inf} (µg.h/mL)	76.8 ± 10.7 (76.0)	77.0 ± 10.7 (76.3)	99.7	98.1 – 101.2

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding levofloxacin. Accordingly, the test tablet Levofloxacin 750 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Levaquin® (Ortho-McNeil Pharmaceutical, Inc.).

A biowaiver was granted for the additional 250 and 500 mg tablet strengths (Macleods Pharmaceuticals Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Levofloxacin 250 and 500 mg tablets were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be similar.

4. Summary of product safety and efficacy

[TB278 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, [TB278 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Levaquin® (Ortho-McNeil Pharmaceutical, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB278 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 [TB278 trade name] is used in accordance with the SmPC**.**

Bioequivalence

[TB278 trade name] has been shown to be bioequivalent with Levaquin® (Ortho-McNeil Pharmaceutical, Inc.)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB278 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 [TB278 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 would allow inclusion of [TB278 trade name] manufactured at Macleods Pharmaceuticals Limited, Block-N2, Village Theda, Post Office Lodhimajra, Tehsil Baddi, District Solan, Himachal Pradesh – 174101, India in the list of prequalified medicinal products.