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	[TB205 trade name][*]
Manufacturer of Prequalified Product	Cipla Ltd, Unit VII, III, IV Plot No: L-147 to L147-1 & L139 to L-146 Verna Industrial Estate, Goa – 403722, India
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin
Pharmaco-therapeutic group (ATC Code)	Antibacterial for systemic use, fluoroquinolone, (J01MA12)
Therapeutic indication	[TB205 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* [TB205 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

[TB205 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis. [TB205 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.

[TB205 trade name] should be prescribed by a physician experienced in the management of tuberculosis infection.

2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

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-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid hemihydrate. It is a class 1 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*). The API is thus BCS highly soluble.

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.

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

The API specifications include tests for description, solubility, identification, water content, specific optical rotation, residue on ignition, heavy metals, assay (HPLC), related substances (HPLC), enantiomeric impurity (chiral HPLC), residual solvents 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 corn starch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and povidone. The commercially sourced proprietary film-coating mixture contains erythrosine aluminum lake, hypromellose, iron oxide black, iron oxide red, polyethylene glycol and titanium dioxide. TSE/BSE free certification has been provided for magnesium stearate.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Levoflox 250 tablets are pink, capsule shaped, biconvex, film-coated tablets with central break-line on one side and plain on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in a HDPE bottle sealed with aluminium foil and fitted with continuous thread polypropylene closure, containing absorbent cotton, and in PVC-aluminium blisters.

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

The development of the final composition of product has been described. The aim was to develop tablets, which would be bioequivalent to the comparator product, Tavanic® 250 mg film-coated tablets. The excipients used in the formulation design were selected from prior knowledge and variability with respect to physicochemical and functional properties, supported by API-excipient compatibility studies. Analysis of the comparator product identified a quality target product profile that included dissolution profiles in the BCS media, as well as other aspects of product quality and equivalence.

For manufacture of the core tablets a conventional wet granulation process was selected. A series of experiments were conducted in order to obtain a tablet with the desired physical characteristics, including dissolution profiles comparable with the comparator product. 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 description, identification of the API, average weight, uniformity of dosage units, water content (KF), dissolution (UV detection), related substances (HPLC), assay (HPLC) and microbiological examination of non-sterile products.

Stability testing

Stability studies have been conducted on three batches in each packaging configuration at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions. The product proved to be quite stable at both storage conditions. 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 bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

Bioequivalence study comparing levofloxacin 500 mg tablet of Cipla Ltd., India with Tavanic® tablet (containing levofloxacin 500 mg) of Aventis Pharma, Germany in healthy human subjects under fasting conditions (study no. 06-10-082).

The objective of the study was to compare the bioavailability of the stated levofloxacin 500 mg tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Tavanic®, Aventis Pharma) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – Levofloxacin 500 mg tablet (levofloxacin 500 mg) Batch no. G76412.

Treatment R: Reference – Tavanic® 500 mg tablet (levofloxacin 500 mg) Batch no. 40E965.

A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 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 analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/mL.

The study was performed with 28 participants; data generated from a total of 25 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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)	1.40 ± 0.95	1.39 ± 0.98	–	–
C_{max} (µg /mL)	6.60 ± 2.48 (6.21)	6.41 ± 1.69 (6.20)	99.8	91.4 – 108.9
AUC_{0-t} (µg h/mL)	53.73 ± 8.75 (53.07)	51.84 ± 7.14 (51.37)	103.4	100.1 – 106.7
AUC_{0-inf} (µg h/mL)	55.48 ± 8.72 (54.84)	53.62 ± 7.07 (53.18)	103.2	100.0 – 106.4

Conclusions

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 500 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Tavanic® (Aventis Pharma).

The results of the bioequivalence study were used to support the application for the test tablet [TB205 trade name]. A biowaiver was granted for this [TB205 trade name] (Cipla Ltd., India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Levofloxacin 250 mg tablet strength was 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 API were determined to be similar.

4. Summary of product safety and efficacy

[TB205 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality [TB205 trade name] is a direct scale-down of Levoflox 500 tablets (levofloxacin 500 mg tablets). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Tavanic® 500 mg tablets (containing 500 mg levofloxacin) for which benefits have been proven in terms of clinical efficacy.

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 [TB205 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB205 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, [TB205 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB205 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 to include [TB205 trade name], manufactured at Cipla Ltd, Unit VII, III, IV, Plot No: L-147 to L147-1 & L139 to L-146, Verna Industrial Estate, Goa 403722, India in the list of prequalified medicinal products.