This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Oflox 400 Tablets*
Manufacturer of Prequalified Product:	Cipla Ltd, Patalganga Unit II Manufacturing division Plot no. A - 42 Patalganga Industrial Area, District - Raigad 410220 Patalganga Maharashtra India Tel : + 91 2192 50811
Active Pharmaceutical Ingredient (API):	ofloxacin
Pharmaco-therapeutic group (ATC Code):	Antibacterial for systemic use, fluoroquinolone (J01MA01)
Therapeutic indication:	Oflox 400 Tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. Oflox 400 Tablets is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance, and should only be used when other recommended fluoroquinolone options are not available.

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Oflox 400 Tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.* Oflox 400 Tablets is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance, and should only be used when other recommended fluoroquinolone options are not available.

Oflox 400 Tablets 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)

Ofloxacin 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.

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control quality of the API.

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, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate and sodium starch glycolate. The commercially sourced proprietary film-coating mixture contains hypromellose, iron oxide yellow, polyethylene glycol and titanium dioxide. TSE/BSE free certifications have been provided for lactose and magnesium stearate.

Finished pharmaceutical product (FPP)

Product specifications
The finished product specifications are pharmacopoeial based and include tests for description, identification of the API and colorants, average weight, content uniformity, water content (KF), dissolution (UV detection), disintegration time, degradation products (HPLC), assay (HPLC), specific optical rotation (to distinguish API from levofloxacin) and microbial examination of non-sterile products.

Pharmaceutical development and manufacture
Oflox 400 Tablets are pale, yellowish-white coloured, capsule shaped, biconvex, film-coated tablets with central break-line on one side and plain on 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 HDPE bottles (different pack sizes) with screw cap, containing a silica gel bag and rayon sanicoil, and in PVC-aluminium blisters.

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, Tarivid® 400 mg tablets. The excipients used in the formulation design were selected from prior knowledge and variability with respect to physicochemical and functional properties and excipients present in the comparator product, 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.

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.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2008 according to internationally accepted guidelines.

Bioequivalence study comparing Ofloxacin 400 mg tablet of Cipla Ltd., India with Tarivid® 400 mg tablet (containing Ofloxacin 400 mg) of Aventis Pharma, Germany in healthy human subjects under fasting conditions (study no. 06-11-086).

The objective of the study was to compare the bioavailability of the stated Ofloxacin 400 mg tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Tarivid®, Aventis Pharma) and to assess bioequivalence. The comparison was performed as a single centre, 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 – Ofloxacin 400 mg tablet (ofloxacin 400 mg) Batch no. KW8015.
Treatment R:	Reference – Tarivid® 400 mg tablet (ofloxacin 400 mg) Batch no. 40E633.

A 6 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 36 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 ofloxacin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml.

The study was performed with 24 participants; data generated from a total of 23 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Ofloxacin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.02 ± 0.52	1.07 ± 0.46	-	-
C_{max} (µg/ml)	5.77 ± 1.28 (5.65)	5.86 ± 1.38 (5.70)	98.6	91.0 – 106.8
AUC_{0-t} (µg.h/ml)	38.51 ± 4.48 (38.27)	40.33 ± 5.87 (39.92)	95.8	93.6 – 98.1
AUC_{0-inf} (µg.h/ml)	39.64 ± 4.68 (39.38)	41.38 ± 6.06 (40.96)	96.1	94.0 – 98.2

* geometric mean

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ofloxacin. Accordingly, the test tablet Ofloxacin 400 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Tarivid® (Aventis Pharma).

4. Summary of Product Safety and Efficacy

Oflox 400 Tablets 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 and bioavailability Oflox 400 Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Tarivid® (ofloxacin 400 mg tablets) 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 Oflox 400 Tablets is used in accordance with the SmPC.

Bioequivalence

Oflox 400 Tablets has shown to be bioequivalent with Tarivid® 400 mg tablets (Aventis Pharma, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, Oflox 400 Tablets 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 Oflox 400 Tablets 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 Oflox 400 Tablets, manufactured at Cipla Ltd, Patalganga Unit II, Manufacturing division Plot no. A – 42, Patalganga Industrial Area, District – Raigad, 410220 Patalganga, Maharashtra, India in the list of prequalified medicinal products.