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:	STAXOM*
Manufacturer of Prequalified Product:	MSN Laboratories Private Limited (Formulations division) Plot No. 42, Anrich Industrial Estate Bollaram, Medak District Pin code- 502 325, Andhra Pradesh, India.
Active Pharmaceutical Ingredient (API):	Moxifloxacin
Pharmaco-therapeutic group (ATC Code):	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication:	STAXOM is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

STAXOM is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

STAXOM 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)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified moxifloxacin (up to 400mg oral dose) as a BCS class 1 API, eligible for BCS-based biowaiver applications. 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 lactose monohydrate, povidone, lactose anhydrous, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The film coat contains hypromellose, titanium dioxide, macrogol and iron oxide red. A TSE/BSE free declaration has been provided for each excipient.

Finished pharmaceutical products (FPP)

Pharmaceutical development and manufacture
Moxifloxacin (as hydrochloride) 400mg Tablets are caplet shaped, brick-red coloured, smooth film-coated tablets plain on both sides. The tablets are presented in PVC/PVDC-Alu blisters packs.

The development of the final composition of multisource product has been described. The aim was to develop tablets which would be bioequivalent to the comparator product, Avalox® 400 mg film-coated tablets. The comparator product was characterized in support of the development and for defining a quality target product profile. The selection of excipients in the formulation was based on their compatibility with moxifloxacin hydrochloride and their suitability to achieve the desired characteristics of the tablets.

For manufacture of the core tablets a conventional wet granulation process was selected. The formulation and process parameters were optimised and dissolution profiles similar to the comparator product were obtained. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications
The finished product specifications are regarded adequate for ensuring consistent quality of the product and include tests for description, identification of the API (HPLC, UV) and colorants, average weight, uniformity of weight, tablet dimensions, hardness, disintegration time, water content, dissolution (UV detection), uniformity of dosage units (by mass variation), related substances (HPLC), assay (HPLC) and microbial limits. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. 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 2010 according to internationally accepted guidelines:

An open label, balanced, randomized, two-treatment, two-period, two- sequence, single-dose, crossover bioequivalence study comparing moxifloxacin hydrochloride 400 mg tablets of MSN Laboratories Limited with Avelox® 400 mg film coated tablets (containing moxifloxacin hydrochloride 400 mg) of Bayer, in healthy, adult human subjects under fasting conditions (study no. 2005/10).

The objective of the study was to compare the bioavailability of the stated Moxifloxacin 400 mg tablet manufactured by MSN Laboratories Limited, India (test drug) with the same dose of the reference formulation (Avelox®, Bayer Schering Pharma AG) 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 – 1 tablet Moxifloxacin 400 mg (moxifloxacin 400 mg) Batch no. 041009002.
Treatment R:	Reference – 1 tablet Avelox® (moxifloxacin 400 mg) Batch no. BFX5VT1.

A 17 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 samples within 96 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 moxifloxacin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/ml for moxifloxacin.

The study was performed with 24 participants; data generated from a total of 21 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Moxifloxacin

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)	1.18 ± 0.63	1.14 ± 0.47	-	-
C_{max} (ng/ml)	2624 ± 402 (2595)	2647 ± 306 (2630)	98.1	92.9 – 103.6
AUC_{0-t} (ng.h/ml)	27467 ± 3497 (27254)	26834 ± 4164 (26519)	102.2	98.8 – 105.8
AUC_{0-inf} (ng.h/ml)	28530 ± 3616 (28309)	27835 ± 4193 (27526)	102.4	99.3 – 105.5

* geometric mean

Conclusion

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

4. Summary of Product Safety and Efficacy

STAXOM 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 STAXOM is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Avelox® 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 STAXOM is used in accordance with the SmPC.

Bioequivalence

STAXOM has shown to be bioequivalent with Avelox® 400 mg tablets Bayer Schering Pharma AG, Germany.

Efficacy and Safety

Regarding clinical efficacy and safety, STAXOM 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of STAXOM was acceptable for the following indication: "**in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis"** and has advised that the quality, efficacy and safety of STAXOM allow inclusion of STAXOM, manufactured at MSN Laboratories Limited (Formulations division), Plot No. 42, Anrich Industrial Estate, Bollaram, Medak District,Pin code- 502 325, Andhra Pradesh, India in the list of prequalified medicinal products.