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	[TB315 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Ltd, Unit 5 Sy No 439, 440, 441 & 458 TSIIC Formulation SEZ Polepally Village Jadcherla (M) Mahaboob Nagar District Telangana – 509 301 India
Active Pharmaceutical Ingredient(s) (API)	Moxifloxacin
Pharmaco-therapeutic group (ATC Code)	Quinolone antibacterials, Fluoroquinolones (J01MA14)
Therapeutic indication	[TB315 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB315 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB315 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.

[TB315 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)

Based on scientific principles the WHO Prequalification Team – Medicines has identified moxifloxacin (as hydrochloride) up to 400mg oral dose as a BCS class 1 API, eligible for BCS-based biowaiver applications. The API is thus regarded highly soluble in terms of the BCS.

Moxifloxacin hydrochloride, 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride is a slightly hygroscopic, light yellow or yellow substance. The API contains two stereogenic carbon centres, with the desired stereochemistry (4aS,7aS) built into one of the starting materials. It is known to exhibit polymorphism. The manufacturing process consistently produces an monohydrate form, which is characterised by XRPD.

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

The specifications of moxifloxacin hydrochloride are pharmacopoeial based and include tests for appearance, solubility, identification of the API (IR, specific optical rotation, XRPD) and chloride counter ion, appearance of solution, pH, related substances (HPLC and UFLC-MS), water (KF), sulfated ash, heavy metals, hydrochloride content (potentiometric), assay (HPLC), palladium and nickel content (AAS), residual solvents (GC), particle size and microbial limits.

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, croscarmellose sodium, colloidal anhydrous silica, povidone and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, iron oxide red and iron oxide yellow. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink coloured, capsule shaped, biconvex, film coated tablet debossed with '80' on one side and 'I' on the other side. The tablets are presented in Alu-Alu blisters cards. The product was developed as an immediate release, solid oral tablet dosage form that would be comparable with the WHO recommended comparator product Avalox® 400 mg tablets in terms of performance and stability. The excipients selected for the core tablets are conventional pharmaceutical ingredients, included in the formulation at suitable levels for recognised purposes. The compatibility of the excipients with the API was demonstrated by API-excipient studies performed on binary mixtures.

Wet granulation was selected to overcome the poor flowability observed in trial batches. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (HPLC, TLC, UV) and colorants, average weight, water content (KF), uniformity of dosage units (by weight variation), dissolution (UV detection), related compounds (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition 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 2011 according to internationally accepted guidelines.

Study title: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Moxifloxacin Hydrochloride 400 mg tablets of Hetero Labs

Limited, Hyderabad, India and Avalox® (moxifloxacin hydrochloride) 400 mg tablets of Bayer Schering Pharma, UK, in healthy human adult subjects, under fasting conditions (study no. 2562/11).

The objective of the study was to compare the bioavailability of [TB315 trade name], manufactured for/by Hetero Labs Limited, India (test drug) with the reference formulation Avalox® (Bayer Schering Pharma) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomised, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomised fashion:

Treatment T: Test – 1 tablet [TB315 trade name]
(moxifloxacin (as hydrochloride) 400 mg)
Batch no. J100072

Treatment R: Reference – 1 tablet Avalox®
(moxifloxacin (as hydrochloride) 400 mg)
Batch no. ITA07RB

A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 60 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for moxifloxacin.

The study was performed with 36 participants; data generated from a total of 35 subjects were utilised 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 table:

Moxifloxacin

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)	2.11 ± 1.12	1.95 ± 0.96	–	–
C_{max} (µg/mL)	1.92 ± 0.40 (1.89)	1.95 ± 0.46 (1.91)	99.1	95.3 – 103.0
AUC_{0-t} (µg·h/mL)	28.3 ± 4.5 (27.9)	27.9 ± 4.5 (27.6)	101.3	99.4 – 103.3
AUC_{0-inf} (µg·h/mL)	29.6 ± 4.7 (29.3)	29.3 ± 4.7 (29.0)	101.1	99.1 – 103.0

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 [TB315 trade name] 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).

4. Summary of product safety and efficacy

[TB315 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 and bioavailability [TB315 trade name] 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 [TB315 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB315 trade name] has shown to be bioequivalent with Avalox® 400 mg tablets ,Bayer Schering Pharma , U.K.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB315 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 [TB315 trade name] was acceptable for the following indication: 'in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*', and would allow inclusion of [TB315 trade name], manufactured at Hetero Labs Limited, Unit 5, Survey No 439,440,441 & 458 TSIIC Formulation SEZ, Polepally Village, Jadcherla (M), Mahaboob Nagar District, Telangana - 509 301, India in the list of prequalified medicinal products.