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	[TB378 trade name]*
Manufacturer of Prequalified Product	Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin
Pharmaco-therapeutic group (ATC Code)	Antibacterial for systemic use, fluoroquinolone, J01MA12
Therapeutic indication	[TB378 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

1. Introduction

[TB378 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to Mycobacterium tuberculosis.

It is also indicated as monotherapy for the prevention of multidrug-resistant tuberculosis in persons at risk.

The therapy should be initiated 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-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Based on scientific principles WHO PQTm has identified levofloxacin (up to 750 mg oral dose) as a BCS class 1 API. Levofloxacin is thus highly soluble according to the BCS.

The API specifications include tests for appearance, identification (IR, HPLC), assay (HPLC), inorganic impurities (residue on ignition), related substances (HPLC), specific optical rotation, water content, residual solvents (GC) 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.

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and hydroxypropyl methyl cellulose. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol- part hydrolyzed, titanium dioxide, talc, macrogol/polyethylene glycol, lecithin (soya), FD&C yellow #5/tartrazine aluminium lake, FD&C yellow #6/sunset yellow FCF aluminium lake and FD&C blue #2/indigo carmine aluminium lake. None of the excipients are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a pink, oval, film- coated tablet with yellowish-white or light-yellow core, debossed with "KY002" on one side and a scoreline on the other side. The scoreline is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in PVC-Alu blister packs.

Two tablet strengths proportionally similar in composition with regards to the core tablets were developed; 250mg and 500mg.

The development of the final composition of the multisource product has been described. The objective was to develop a solid oral dosage form which is stable, pharmaceutically equivalent and bioequivalent to the WHO recommended comparator product, Levaquin® 500mg tablets (Janssen Pharms, US). The quality target product profile was defined based on the properties of the API, comparator product characterization and selection of suitable excipients. Due to the poor flow properties but good chemical stability of the API, wet granulation manufacturing process was selected for the finished pharmaceutical product. Various studies were performed to optimize the concentration of the functional excipients and process parameters to obtain a product of desired characteristics and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.
According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification (HPLC, UV), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by mass variation), moisture content, related substances (HPLC), weight variation (whole and half tablet) and microbial limits.

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 conditions in the packaging proposed for marketing of the product. The data provided indicates that the product is stable at both storage conditions, showing no out -of- specification results for all the parameters tested. 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

No bioequivalence study has been performed. As levofloxacin is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Levaquin ® 500 mg tablet (Janssen Pharms, US) and the test Levofloxacin 500 mg tablet (Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd.) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 have been shown. Accordingly, the test tablet Levofloxacin 500 mg (Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd.) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the respective reference Levaquin ® 500 mg tablet (Janssen Pharms, US).

4. Summary of product safety and efficacy

[TB378 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, [TB378 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Levaquin ® 500 mg tablet (Janssen Pharms, US for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB378 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 [TB378 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB378 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB378 trade name] and Levaquin ® 500 mg tablet (Janssen Pharms, US) are bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB378 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 [TB378 trade name] was acceptable for the following indication: 'in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* ', and would allow inclusion of [TB378 trade name], manufactured at Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd, 333 Jiangnan Second Road, Hengdian, Dongyang, Zhejiang province, P.R. China in the list of prequalified medicinal products.