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	[TB373 trade name][*]
Manufacturer of Prequalified Product	PT. Caprifarmindo Laboratories Jl. Industri Cimareme No. 8 Block H, Desa Cipeundeuy Kecamatan Padalarang Kabupaten Bandung Barat Indonesia
Active Pharmaceutical Ingredient(s) (API)	Levofloxacin (as hemihydrate)
Pharmaco-therapeutic group (ATC Code)	Fluoroquinolones (J01MA12)
Therapeutic indication	[TB373 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.

1. Introduction

[TB373 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.

[TB373 trade name] should be initiated by a healthcare 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 hemihydrate has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB373 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API

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

prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose and magnesium stearate, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and colour FD& C red # 40 (Allura red). None of the excipients is of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink-coloured, round, biconvex, film-coated tablet, with a 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 aluminium-aluminium strips.

The objective of the formulation development strategy was to develop a product with a similar quality profile to that of the WHO recommended comparator product, Levaquin® 500mg film-coated tablets. The quality target product profile and critical quality attributes were established. The excipients selected were the same as in the composition of the WHO recommended comparator product. Levofloxacin hemihydrate is stable to heat and moisture however it has poor flowability, therefore a wet granulation manufacturing process was selected to improve the flow properties of the granules. Formulation trials were performed to optimise the concentration of excipients and process parameters. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications are pharmacopoeia based and include tests for description, moisture content, tablet weight, disintegration time, strip leakage, identification (HPLC and IR), uniformity of dosage unit (weight variation), dissolution (UV detection), assay (HPLC), residual solvent (GC), organic impurities (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided shows that the product is stable at these storage conditions. Based on the available 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 of the reference product Levaquin® 500 mg tablets (Janssen Pharmaceuticals Inc.) and the test product Levofloxacin 500 mg tablets (PT Sanbe Farma), with respect to qualitative and quantitative composition of the formulations, has been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 has been shown. Accordingly, the test tablet Levofloxacin 500 mg (PT Sanbe Farma) meets the criteria for a BCS-based biowaiver and is therefore, considered bioequivalent to the respective reference Levaquin® 500 mg tablet (Janssen Pharmaceuticals Inc.).

4. Summary of product safety and efficacy

[TB373 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 in vitro dissolution, [TB373 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Levaquin® (Janssen Pharmaceuticals Inc.), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB373 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 [TB373 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB373 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [TB373 trade name] and Levaquin® (Janssen Pharmaceuticals Inc.) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB373 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 [TB373 trade name] was acceptable for the following indication: 'treatment or prevention of multidrug-resistant tuberculosis due to *Mycobacterium tuberculosis*', and would allow inclusion of [TB373 trade name], manufactured at PT. Caprifarmindo Laboratories, Jl. Industri Cimareme No. 8, Block H, Desa Cimareme, Kecamatan Padalarang, Kabupaten, Bandung Barat, Indonesia in the list of prequalified medicinal products.