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:	[TB354 trade name] *
Manufacturer of Prequalified Product:	PT. Kalbe Farma Line 8A Kawasan Industri Delta Silicon Jl. M.H. Thamrin Blok A3-1 Lippo Cikarang, Bekasi, 17550 Indonesia
Active Pharmaceutical Ingredient (API):	Levofloxacin
Pharmaco-therapeutic group (ATC Codes):	Antibacterials for systemic use, Quinolone antibacterials, Fluroquinolones (Levofloxacin): J01MA12)
Therapeutic indication:	[TB354 trade name] is used, in combination with other antituberculosis drugs, for: 1. First line treatment of rifampicin-sensitive, isoniazid-resistant tuberculosis 2. Multi-drug resistant tuberculosis (MDR-TB) It should be used only if first-line drugs for treating tuberculosis are inappropriate due to resistance.

1. Introduction

[TB354 trade name] is used, in combination with other antituberculosis drugs, for first line treatment of rifampicin-sensitive, isoniazid-resistant tuberculosis and multi-drug resistant tuberculosis (MDR-TB)
It should be used only if first-line drugs for treating tuberculosis are inappropriate due to resistance. [TB354 trade name] should be initiated by a health care provider experienced in the management of tuberculosis.

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 Levofloxacin 500mg Film-coated Tablets is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two

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

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 hypromellose, crospovidone, microcrystalline cellulose and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol / macrogol and lecithin. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an oval shallow convex film coated tablet, white colour, embossed with "KALBE" on one side and scored on the other side. The score 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 an aluminium strip, such 3 strips are packed in a mono carton.

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 selection of excipients was based on the composition of the WHO recommended comparator product, prior study of existing product for local market and API-excipient compatibility. Since Levofloxacin is quite a fine material, in order to improve compressibility and flowability properties, wet granulation was selected as a method of manufacture of the tablets. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, individual weight, weight variation, disintegration time, moisture content (KF), identification of levofloxacin (HPLC & Spectrophotometry UV-VIS), assay (HPLC), dissolution (Spectrophotometry UV-VIS), organic impurities and microbiological examination. 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 product proved to be quite stable at these conditions, with no apparent negative trend. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

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 Pharmaceutical Inc.) and the test Levofloxacin 500 mg tablet (P.T. Kalbe Farma Tbk, Lippo Cikarang, Bekasi, Indonesia) 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 has been shown. Accordingly, the test tablet Levofloxacin 500 mg tablet (P.T. Kalbe Farma Tbk, Lippo Cikarang, Bekasi, Indonesia) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the reference Levaquin® 500 mg tablet (Janssen Pharmaceutical Inc.).

4. Summary of Product Safety and Efficacy

[TB354 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [TB354 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance.

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 [TB354 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB354 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB354 trade name] 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 [TB354 trade name] was acceptable for the following indication: “first line treatment of rifampicin-sensitive, isoniazid-resistant tuberculosis and multi-drug resistant tuberculosis (MDR-TB)”, and has advised that the quality, efficacy and safety of [TB354 trade name] allow inclusion of [TB354 trade name], manufactured at PT. Kalbe Farma Line 8A, Kawasan Industri Delta Silicon, Jl. M.H. Thamrin Blok A3-1, Lippo Cikarang, Bekasi, 17550, Indonesia in the list of prequalified medicinal products.