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:	[TB326 trade name][1]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block-N2 Village Theda P.O. Lodhimajra Tehsil Baddi District Solan Himachal Pradesh – 174101 India
Active Pharmaceutical Ingredient (API):	Levofloxacin hemihydrate
Pharmaco-therapeutic group (ATC Code):	Antibacterial for systemic use, fluoroquinolone, (J01MA12)
Therapeutic indication:	[TB326 trade name] is indicated, in combination with other antituberculosis agents, for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in children [TB326 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.

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

1. Introduction

[TB326 trade name] is indicated in combination with other antituberculosis agents, for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in children. [TB326 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.

[TB326 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)

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-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Based on scientific principles the WHO PQT-M has identified levofloxacin (up to 750 mg oral dose) as a BCS class 1 API. Levofloxacin is thus highly soluble in aqueous medium over the physiological pH range.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC), specific optical rotation, water content (KF), residue on ignition, heavy metals, organic impurities (HPLC), enantiomeric purity (chiral HPLC; ≤ 0.8%), assay (HPLC) and residual solvents.

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 tablet formulation include hydroxypropylcellulose, ethylcellulose, microcrystalline cellulose, crospovidone, sodium chloride, trisodium citrate dihydrate, citric acid monohydrate, aspartame, sucralose, peppermint flavour powder, orange flavour powder and magnesium stearate. No material derived from or exposed to animals infected by TSE/BSE is used in the manufacture of the dispersible tablets.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is an off-white to pale yellow-coloured, capsule-shaped, biconvex, uncoated tablet, having a break-line on one side and plain surface 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 presented in Alu/Alu cold form blister packs or Alu/Alu strip packs. The primary packaging serves to protect the tablets form moisture and light.

The objective of the development activities was to obtain a formulation of the dispersible tablets that would be bioequivalent to the WHO recommended comparator product, Tavanic® 250 mg film-coated tablets. The selection of excipients in the formulation of the dispersible tablets was based on their demonstrated compatibility with levofloxacin hemihydrate, similarly with the comparator product and their suitability to achieve the desire characteristics of the formulation. As the dosage form is a dispersible tablet, sweeteners and flavouring agents may play an important role for patient acceptance. Aspartame and sucralose were selected as sweeteners, complemented by peppermint and orange flavours. Sodium chloride, citric acid monohydrate and trisodium citrate dihydrate were included as taste modifiers to mask the bitter after taste.

The wet granulation method, using organic solvents, was selected as the manufacturing process for the dispersible tablets. Various studies were performed to optimize the concentration of the functional excipients and process parameters to obtain a product of desired characteristics, including acceptability and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for tablet description, identification (IR, UV), average weight, friability, hardness, disintegration time, fineness of dispersion, loss on drying, subdivision of tablets, uniformity of dosage units (by content uniformity), dissolution (UV detection), related substances (HPLC), assay (HPLC), residual solvents and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, showing no significant trend, negative trend or out-of-specification result for all parameters tested. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

The reconstituted preparation (tablets dispersed in water) should be consumed within 10 minutes.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2015/2016 according to internationally accepted guidelines.

Study title: Bioequivalence study of five tablets as single dose of Levofloxacin dispersible tablets 100 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with two tablets of Tavanic® (levofloxacin) tablets 250 mg marketed by Sanofi-Aventis Netherlands B.V. Europe in healthy, adult, human subjects under fasting condition (study no. BEQ-1535-LEVO-2015).

The objective of the study was to compare the bioavailability of the stated Levofloxacin 100 mg Dispersible Tablets manufactured for/by Macleods Pharmaceuticals Ltd., India (test formulation) with the reference formulation Tavanic® (Sanofi-Aventis Netherlands B.V. Europe) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T:	Test – 5 dispersible tablets Levofloxacin 100 mg (levofloxacin 500 mg) Batch no. BLB5503A
Treatment R:	Reference – 2 tablets Tavanic® (levofloxacin 500 mg) Batch no. 3EK2X

The dispersible test tablets were dispersed in 50 mL of water and administered with a total of 240 mL water (including the rinsing water). The reference tablets were not dispersed and administered with 240 mL water. A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 48 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 levofloxacin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/mL for levofloxacin.

The study was performed with 27 participants; data generated from a total of 26 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Levofloxacin

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 (ANOVA log)
t_{max} (h)	0.91 ± 0.49	1.08 ± 0.46	-	-
C_{max} (ng/mL)	5210 ± 968 (5150)	5837 ± 1534 (5627)	91.5	84.2 – 99.5
AUC_{0-t} (ng.h/mL)	42211 ± 7597 (41630)	43505 ± 8365 (42938)	97.0	95.1 – 98.9
AUC_{0-inf} (ng.h/mL)	44401 ± 7255 --	45361 ± 8407 --	-	-

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding levofloxacin. Accordingly, the test levofloxacin 100 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the reference Tavanic® (Sanofi-Aventis).

4. Summary of product safety and efficacy

[TB326 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, [TB326 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product (Tavanic®, Sanofi-Aventis), for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB326 trade name] is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics (SmPC) 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 [TB326 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB326 trade name] has shown to be bioequivalent with Tavanic® (Sanofi-Aventis, Netherlands).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB326 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB326 trade name] was acceptable for the following indication: "as a second-line antimycobacterial drug , in combination with other

antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in children." and has advised that the quality, efficacy and safety of [TB326 trade name] allow inclusion of [TB326 trade name], manufactured at Macleods Pharmaceuticals Limited, Block-N2, Village Theda, Post Office Lodhimajra, Tehsil Baddi, District Solan, Himachal Pradesh – 174101, India in the list of prequalified medicinal products.