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	[TB408 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited (FDF Unit 2) H-12 & H-13, MIDC, Waluj Chhatrapati Sambhajinagar - 431136 Maharashtra State India.
Active Pharmaceutical Ingredient (API)	Bedaquiline (as fumarate)
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, drugs for treatment of tuberculosis (J04AK05)
Therapeutic indication	[TB408 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

1. Introduction

[TB408 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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)

Bedaquiline fumarate has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use 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 [TB408 trade name], 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 components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Additional user requirements for the API include test for particle size distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, corn starch, hypromellose, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'V' debossed (stamped into) one side and 'BA' on the other side.

The tablets are packaged in aluminium foil on aluminium foil cold form blister cards and round, opaque white plastic (HDPE) bottles. Each bottle also contains a piece of cotton wool to keep the tablets in place. Each bottle has an aluminium foil seal and a white opaque childproof plastic (polypropylene) screw cap.

The objective of the formulation development strategy was to obtain a robust, stable immediate release product bioequivalent to the WHO recommended comparator product, Sirturo® (bedaquiline fumarate) tablets. The comparator product was characterized and on that basis a quality target product profile was defined; critical quality attributes were also identified. The excipients were selected based on the comparator product and API-excipient compatibility data. Due to the poor flowability of the API, a wet granulation method was selected for manufacturing the product. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. 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 include tests for description, identification (HPLC, UV and TLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition in the packages proposed for marketing of the product. The data provided indicated that the tested parameters remained within acceptable limits at both storage conditions, with no obvious trend or variability. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable. The in-use storage period as indicated in the product information for the bottle pack is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2023 according to internationally accepted guidelines.

Single dose fed oral bioequivalence study of Bedaquiline tablets 100 mg of Mylan Laboratories Limited, India with Sirturo® 100 mg tablets of Janssen-Cilag International NV., in healthy adult human subjects (study no. BEDA-TBZ-1003).

The objective of the study was to compare the bioavailability of the stated Bedaquiline 100 mg tablet manufactured by Mylan Laboratories Limited, India (test drug) with the reference formulation Sirturo® 100 mg tablet (Janssen-Cilag International NV) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Bedaquiline 100 mg (bedaquiline 100 mg) Batch no. 2025216.

Treatment R: Reference – 1 tablet Sirturo® 100 mg (bedaquiline 100 mg) Batch no. TMC22008M.

A 39-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 bedaquiline were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 3 ng/mL for bedaquiline.

The study was performed with 36 participants; data generated from a total of 27 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Bedaquiline

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)	5.00 (2.50 – 5.50)	5.00 (3.00 – 5.00)	–	–
C_{max} (ng/mL)	1303 ± 332 (1232)	1237 ± 392 (1180)	104.5	97.3 – 112.2
AUC_{0-t} (ng·h/mL)	15647 ± 4485 (14812)	15579 ± 5194 (14731)	100.6	96.3 – 105.0

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding bedaquiline. Accordingly, the test Bedaquiline 100 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Sirturo® 100 mg tablet (Janssen-Cilag International NV).

4. Summary of product safety and efficacy

[TB408 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, [TB408 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sirturo® 100 mg tablet (Janssen-Cilag International NV). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB408 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 [TB408 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB408 trade name] has been shown to be bioequivalent with Sirturo® 100 mg tablet (Janssen-Cilag International NV).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB408 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 [TB408 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 [TB408 trade name], manufactured at Mylan Laboratories Limited, (FDF Unit 2) H-12 & H-13, MIDC, Waluj, Chhatrapati Sambhajinagar – 431136, Maharashtra State, India in the list of prequalified medicinal products.