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	[TB390 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited 304, Atlanta Arcade, Marol Church road, Andheri (East), Mumbai – 400 059, India Tel.: +91-22-66762800 Fax: +91 -22-28216599
Active Pharmaceutical Ingredients (API)	Bedaquiline (as fumarate)
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, drugs for treatment of tuberculosis (J04AK05)
Therapeutic indication	[TB390 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

1. Introduction

[TB390 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 is a white to off white powder. It is critically insoluble in aqueous media, light sensitive and non-hygroscopic.

From the chemical structure of bedaquiline fumarate, it is evident that it contains two asymmetric carbon atoms therefore four isomers are possible, of which the RS form is pharmaceutically active. The manufacturer consistently produces crystalline form A, which is routinely controlled by p-XRD in the specifications of the API.

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

The API specifications include tests for description, solubility, identification (IR and HPLC), polymorphic form (p-XRD), loss on drying, residue on ignition, related substances (HPLC), fumaric acid content (HPLC), enantiomeric purity (HPLC), assay (HPLC), residual solvents (GC), potential genotoxic impurities (limits are in line with ICH M7) and particle size distribution (PSD). The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

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 lactose monohydrate, corn/maize starch, hypromellose, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. 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 'J' and '47' debossed (stamped into) one side and are plain on the other side. The tablets are packaged in HDPE bottles and aluminium foil on aluminium foil blister cards.

The objective was to develop a stable, robust, immediate release dosage form, bioequivalent to the WHO recommended comparator product, Sirturo® (bedaquiline fumarate) 100 mg tablets. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility data. Due to the micronized nature, poor flowability and high content of the API, wet granulation process was selected for manufacturing to achieve good flowability and homogeneity of the API in the final formulation. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification of API (HPLC and IR), hardness, water content (KF), dissolution (UV detection), uniformity of dosage units (content uniformity), related substances (HPLC), assay (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 condition and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided indicate that all the tested parameters remained within acceptable limits at both storage conditions. 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 after first opening of the bottle is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021 according to internationally accepted guidelines.

Single-dose fed in vivo bioequivalence study of [TB390 trade name] (Macleods Pharmaceuticals Limited, India) to Sirturo® (bedaquiline) tablets 100 mg (Janssen-Cilag International NV, Belgium) in healthy adult, human subjects (study no. BEQ-2703-BEDA-2019).

The objective of the study was to compare the bioavailability of the stated [TB390 trade name] manufactured by/for Macleods Pharmaceuticals 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 [TB390 trade name] (bedaquiline 100 mg) Batch no. BBJ2001A.

Treatment R: Reference – 1 tablet Sirturo® 100 mg (bedaquiline 100 mg) Batch no. TMC20010M.

A 28-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72h 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 10 ng/mL for bedaquiline.

The study was performed with 24 participants; data generated from a total of 23 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)	5.8 ± 1.0	5.4 ± 1.4	–	–
C_{max} (ng/mL)	1011 ± 325 (954)	979 ± 336 (923)	103.3	91.7 – 116.4
$AUC_{0\text{-}72h}$ (ng·h/mL)	13006 ± 3050 (12613)	13301 ± 3977 (12658)	99.7	95.2 – 104.3

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 [TB390 trade name] 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

[TB390 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, [TB390 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 [TB390 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 [TB390 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB390 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, [TB390 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 [TB390 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 [TB390 trade name], manufactured at Macleods Pharmaceuticals Limited, Block N2, Village Theda, Post Office Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.