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	[TB395 trade name][*]
Manufacturer of Prequalified Product	MSN Laboratories Private Limited Formulations Division (Block-D), Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Ranga Reddy (District), Telangana 509228, India
Active Pharmaceutical Ingredient(s) (API)	Bedaquiline (as fumarate)
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, drugs for treatment of tuberculosis (J04AK05)
Therapeutic indication	[TB395 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

1. Introduction

[TB395 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 almost 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.

The API specifications include tests for description, solubility, identification (IR and chiral HPLC), water content (KF), fumaric acid content (by potentiometry), residue on ignition, related substances (HPLC), assay (HPLC), chiral purity (HPLC), residual solvents (GC), polymorphic form (p-XRD)

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

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, maize starch, hydroxypropyl methylcellulose, 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 'MB 1' debossed (stamped into) one side and is 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 poor flowability and the tendency of the micronized API to form agglomerates and adhere to the manufacturing equipment, the risk on assay and content uniformity were mitigated by using a wet granulation process 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. Satisfactory in-process controls have been established.

A risk assessment has been performed and a risk for nitrosamine impurities has been identified within the FPP manufacture. Confirmatory testing has been performed and N- nitroso desmethyl bedaquiline impurity was identified. A test for this impurity has been included in the FPP specifications.

Specifications

The finished product specifications include tests for description, identification of API (UV and HPLC), average weight, disintegration time, water content (KF), uniformity of dosage units (content uniformity), dissolution (UV detection), assay (HPLC), related substances (HPLC), limit of N- nitroso desmethyl bedaquiline impurity (LCMS; ≤ 0.066ppm) 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 limits with no obvious trend or variability 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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, truncated, two-way cross-over, single oral dose, bioequivalence study of Bedaquiline tablets 100 mg of MSN Laboratories Private Limited, India comparing with Sirturo (bedaquiline) tablets 100 mg of Janssen-Cilag International NV, Belgium., in healthy, adult, human, subjects under fed conditions (study no. 011-BE-2021).

The objective of the study was to compare the bioavailability of the stated Bedaquiline 100 mg tablet manufactured by/for MSN Laboratories Private 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. DRB01222A.

Treatment R: Reference – 1 tablet Sirturo® 100 mg (bedaquiline 100 mg) Batch no. TMC19053A.

A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 5 ng/mL for bedaquiline.

The study was performed with 38 participants; data generated from a total of 36 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 (3.00 – 6.50)	5.00 (2.00 – 7.00)	–	–
C_{max} (ng/mL)	1360 ± 433 (1300)	1518 ± 480 (1445)	89.9	83.8 – 96.5
AUC_{0-t} (ng·h/mL)	18774 ± 5392 (18000)	19810 ± 5882 (18992)	94.8	90.4 – 99.3

4. Summary of product safety and efficacy

[TB395 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, [TB395 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 [TB395 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 [TB395 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB395 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, [TB 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 [TB395 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 [TB395 trade name], manufactured at MSN Laboratories Private Limited, Formulations Division (Block-D), Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Ranga Reddy (District), Telangana 509228, India in the list of prequalified medicinal products.