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	[TB397 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited, Plot No.50 to 54A, SEZ, Phase II, Pithampur, Dist.: Dhar Madhya Pradesh, 454774, India
Active Pharmaceutical Ingredient(s) (API)	Macleods Pharmaceuticals Limited
Pharmaco-therapeutic group (ATC Code)	J04AK08 Drugs for treatment of Tuberculosis
Therapeutic indication	[TB397 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to Mycobacterium tuberculosis in adults and adolescents at least 14 years old.

1. Introduction

[TB397 trade name] (Pretonamid 200 mg tablets) is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* in adults and adolescents at least 14 years old.

Treatment regimens should follow the 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)

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

From the chemical structure of pretomanid it has a single stereogenic center, the S-enantiomer being pharmaceutically active and the R-enantiomer being controlled as an impurity. The API shows polymorphism and the manufacturer consistently produces form I, 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), water (KF), loss on drying, residue on ignition, content of R- enantiomer (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic form (p-XRD), 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, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, 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, oval, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'K31' debossed (stamped into) one side and is plain on the other side. The tablets are packaged in 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, Pretomanid® 200 mg tablets (Mylan Specialty L.P. USA). 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 and poor flowability of the API, a wet granulation process was selected for manufacturing resulting in 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 appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of API (HPLC and HPLC/DAD detection), water content (KF), hardness, dissolution (HPLC detection), uniformity of dosage units (weight variation), 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, showing little change. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable

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 Pretomanid tablets 200 mg (Macleods Pharmaceuticals Limited, India) to Pretomanid tablets 200 mg (Mylan Specialty L.P., USA) in healthy adult, human subjects (study no. BEQ-2965-PRET-2020).

The objective of the study was to compare the bioavailability of the stated Pretomanid 200 mg tablet manufactured by/for Macleods Pharmaceuticals Limited, India (test drug) with the reference formulation Pretomanid® 200 mg tablet (Mylan Specialty L.P.) 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 Pretomanid 200 mg (pretomanid 200 mg) Batch no. RPC2102A.
Treatment R: Reference – 1 tablet Pretomanid® 200 mg (pretomanid 200 mg) Batch no. 8117880.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 pretomanid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 9.8 ng/ml for pretomanid.

The study was performed with 24 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Pretomanid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	6.04 ± 1.70	5.25 ± 1.38	-	-
C_{max} (ng/ml)	2355 ± 367 (2327)	2414 ± 353 (2390)	97.4	94.4 – 100.4
AUC_{0-72h} (µg.h/ml)	83.0 ± 15.3 (81.7)	82.4 ± 15.9 (81.0)	100.9	97.9 – 104.0

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding pretomanid. Accordingly, the test Pretomanid 200 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Pretomanid® 200 mg tablet (Mylan Specialty L.P.).

4. Summary of product safety and efficacy

[TB397 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, [TB397 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Pretomanid® 200 mg tablet (Mylan Specialty L.P.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB397 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 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 [TB397 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB397 trade name] has been shown to be bioequivalent with Pretomanid® 200 mg tablet (Mylan Specialty L.P.)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB397 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 [TB397 trade name] was acceptable for the following indication: for the treatment of drug-resistant tuberculosis due to Mycobacterium tuberculosis in adults and adolescents at least 14 years old, and would allow inclusion of [TB397 trade name], manufactured at Macleods Pharmaceuticals Limited, Pithampur, Dist. Dhar, Madhya Pradesh, 454774, India in the list of prequalified medicinal products.