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	[TB304 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No. H-12 & H-13 MIDC, Waluj Aurangabad - 431136 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Cycloserine
Pharmaco-therapeutic group (ATC Code)	Drugs for the treatment of tuberculosis, Antibiotics (J04AB01)
Therapeutic indication	[TB304 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB304 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

1. Introduction

[TB304 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB304 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB304 trade name] should be prescribed by a health care provider experienced in the management of tuberculosis.

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)

Cycloserine 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

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

cycloserine, used in the manufacture of [TB304 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.

The API is slightly hygroscopic. It is highly soluble in aqueous medium over the physiological pH range, thus control of particle size and polymorphic form is not considered important for the product.

Other ingredients

The capsule fill powder contains talc. The capsule shells contain gelatin, iron oxide red, iron oxide yellow and titanium dioxide, while the imprint ink contains shellac, propylene glycol, black iron oxide and potassium hydroxide. The suppliers of gelatin provided EDQM CEPs demonstrating TSE/BSE-compliance of this excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to creamish pink powder filled in hard shell gelatin capsules with light orange opaque cap and white opaque body, axially imprinted with “MYLAN” over “CS250” in black ink on both cap and body. The capsules are packaged in cold forming blister packs and HDPE bottles with polypropylene screw caps. A canister containing 1 g silica gel as desiccant is included in the bottle pack to protect the moisture sensitive and slightly hygroscopic API from hydrolysis.

A multisource product with similar physical and chemical characteristics to that of the WHO recommended comparator product, Seromycin® of the same strength, has been developed. Similar to the comparator product, the composition of the capsule fill consists only of the API and talc. Due to the moisture sensitive nature and very poor flow properties of cycloserine API, a dry granulation (compaction technique) method was selected as manufacturing process. The final lubricated blend is filled into the empty hard gelatin capsule shells. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications are pharmacopoeial based and include tests for description, identification of the API (HPLC, TLC, chemical) and colourants in the capsule shell, dissolution (HPLC detection), uniformity of dosage units (by weight variation), assay (HPLC), loss on drying, related substances (HPLC), average capsule fill weight and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/60%RH (zone II) as long-term storage condition in the packaging proposed for marketing of the product. No studies were conducted at accelerated condition (40°C/75%RH). The data showed degradation of the API, though within agreed limits. The data provided support the proposed shelf life and storage conditions as defined in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2014 according to internationally accepted guidelines.

Study title: An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of Cycloserine 250 mg capsules (Test) of Mylan

Laboratories Limited, Plot No.H-12 & H-13, MIDC, Waluj Industrial Area, Aurangabad-431136, Maharashtra, India and CycloSERINE (cycloserine) capsules USP 250mg (Reference) of The Chao Center for Industrial Pharmacy & Contract Manufacturing, West Lafayette IN 47906, USA in healthy, adult, human subjects under fasting conditions (study no. 034-14).

The objective of the study was to compare the bioavailability of the stated Cycloserine 250 mg capsules manufactured for/by Mylan Laboratories Limited, India (test drug) with the reference formulation CycloSERINE (The Chao Center for Industrial Pharmacy and Contract Manufacturing) 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 – 1 capsule Cycloserine 250 mg (cycloserine 250 mg) Batch no. 2005853
Treatment R: Reference – 1 capsule CycloSERINE (cycloserine 250 mg) Batch no. 13J0007P

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for cycloserine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 249 ng/mL for cycloserine.

The study was performed with 48 participants; data generated from a total of 42 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Cycloserine

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)	0.50 (0.33 – 3.0)	0.67 (0.33 – 3.0)	–	–
C_{max} (µg./mL)	14.4 ± 5.5 (13.6)	14.3 ± 4.4 (13.8)	99.1	90.9 – 108.0
AUC_{0-t} (µg·h/mL)	224 ± 55 (217)	235 ± 58 (228)	95.6	92.0 – 99.3
AUC_{0-inf} (µg·h/mL)	242 ± 65 (234)	256 ± 72 (246)	95.4	91.9 – 99.1

The results of the study show that the preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding cycloserine. Accordingly, the test Cycloserine Capsules 250mg USP meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference CycloSERINE (The Chao Center for Industrial Pharmacy and Contract Manufacturing).

4. Summary of product safety and efficacy

[TB304 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, [TB304 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product CycloSERINE, for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions stated in the summary of product characteristics 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 [TB304 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB304 trade name] has shown to be bioequivalent with CycloSERINE (The Chao Center for Industrial Pharmacy & Contract manufacturing, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB304 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 [TB304 trade name] was acceptable for the following indication: **"in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis,* as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed"** and has advised that the quality, efficacy and safety of [TB304 trade name] allow inclusion of [TB304 trade name], manufactured at Mylan Laboratories Limited Plot No. H-12 & H-13, MIDC, Waluj, Aurangabad – 431136, Maharashtra, India, in the list of prequalified medicinal products.