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	[TB306 trade name]*
Manufacturer of Prequalified Product	Strides Pharma Science Limited Puducherry (Formulation division) Unit II, R.S. No 32, 33 and 34, PIMS Road Periyakalapet, Puducherry, 605 014 India
Active Pharmaceutical Ingredient(s) (API)	Cycloserine
Pharmaco-therapeutic group (ATC Code)	Drugs for the treatment of tuberculosis, Antibiotics (J04AB01)
Therapeutic indication	[TB306 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis. [TB306 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

1. Introduction

[TB306 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis.

[TB306 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB306 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 used in the manufacture of [TB306 trade name] 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

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

4). This procedure provides an assurance that cycloserine, used in the manufacture of [TB306 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 iron oxide red, FD & C red #3, titanium dioxide, FD & C yellow #6 / Sunset yellow FCF, gelatin and iron oxide black, 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. TSE / BSE Free certification was provided for talc.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a hard gelatin capsule with a red opaque coloured cap and grey opaque coloured body, printed "S" on cap and "455" on body with black ink containing white to pale pink granular powder. The capsules are packaged in Alu-Alu blisters and HDPE bottles with child-resistant screw cap. A sachet filled with silica gel desiccant is included in the bottle pack to protect the moisture sensitive and slightly hygroscopic API from hydrolysis. The pharmaceutical development aimed at developing a formulation similar to the WHO recommended comparator product, Seromycin® of the same strength. The composition of the capsule fill consists only of the API and talc, similar to that of the comparator. Initially different techniques – direct blending, wet granulation and dry granulation – were studied and evaluated for manufacture of the product. Based on process feasibility and comparative results with the comparator product the fill blend is manufactured by compacting the talc separately followed by milling and sifting and then mixing with the cycloserine. 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 API, average weight and average net content of the capsule, locking length of the filled capsule, loss on drying, uniformity of dosage units (by weight variation), dissolution (UPLC detection), assay (UPLC), related substances (UPLC/HPLC), residual solvents and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/60%RH (zone II) as long-term storage condition, at 30°C/75%RH (zone IVb) and at accelerated condition (40°C/75%RH). The data showed significant degradation of the API at the accelerated storage condition and at the zone IVb condition. Excursions above 30°C should thus be avoided and the product should be protected from moisture. 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-period, two-sequence, single dose, two-way crossover, oral bioequivalence study of Cycloserine capsules Ph. Int. 250 mg of Strides Pharma Science Limited,Puducherry., India with Seromycin® (cycloserine) capsules USP 250 mg of The Chao Center for Industrial Pharmacy and Contract Manufacturing, USA in normal healthy adult human subjects under fasting conditions (study no. C13322).

The objective of the study was to compare the bioavailability of the stated Cycloserine Capsules Ph. Int. 250 mg manufactured for/by Strides Pharma Science Limited, Puducherry., India (test drug) with the reference formulation Seromycin® (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. 13HO001B
Treatment R: Reference – 1 capsule Seromycin®
(cycloserine 250 mg)
Batch no. 13H0005P

A 12 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 48 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 202 ng/mL for cycloserine.

The study was performed with 38 participants; data generated from a total of 34 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)	0.94 ± 0.74	0.97 ± 0.98	–	–
C_{max} (µg/mL)	10.2 ± 2.9 (9.8)	10.0 ± 1.9 (9.8)	100.2	94.3 – 106.5
AUC_{0-t} (µg.h·h/mL)	148 ± 29 (145)	151 ± 27 (149)	97.5	94.4 – 100.8
AUC_{0-inf} (µg·h/mL)	177 ± 45 (171)	174 ± 39 (170)	100.8	97.5 – 104.2

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding Cycloserine Capsules Ph. Int. 250 mg. Accordingly, the test capsule Cycloserine Capsules Ph. Int. 250 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Seromycin® (The Chao Center for Industrial Pharmacy & Contract manufacturing).

4. Summary of product safety and efficacy

[TB306 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, [TB306 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Seromycin® for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB306 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 [TB306 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB306 trade name] has been shown to be bioequivalent with Seromycin® (The Chao Center for Industrial Pharmacy & Contract manufacturing).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB306 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 [TB306 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 would allow inclusion of [TB306 trade name], manufactured at Strides Pharma Science Limited ,Puducherry (Formulation division), Unit II, R.S. No 32, 33 and 34, PIMS Road, Periyakalapet, Puducherry, 605 014, India, in the list of prequalified medicinal products.