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	[TB416 trade name][*]
Manufacturer of Prequalified Product	Strides Pharma Science Limited Formulation division unit II RS. No. 32, 33 & 34, PIMS Road, Periykalapet, 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	[TB416 trade name] is indicated in combination with other antituberculosis agents for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*

1. Introduction

[TB416 trade name] is indicated in combination with other antituberculosis agents for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

[TB416 trade name] should be prescribed by a physician 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 in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB416 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredient used in the capsule fill formulation include talc, which is pharmacopoeial controlled. The capsule shell contains iron oxide red, iron oxide black, FD&C red #3/Erythrosine, titanium dioxide, FD&C yellow #6/Sunset yellow FCF and gelatin; while the printing ink contains shellac, propylene glycol and black iron oxide, all being controlled by acceptable specifications. Gelatin is of bovine origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a hard gelatin capsule with an opaque red cap and an opaque grey body. The capsules are printed in black on the cap with 'S' and on the body with '455'. They contain a white to pale pink granular powder. The hard gelatin capsules are packaged in aluminium foil blister cards and HDPE bottle packs.

The development of the final composition of the multisource product has been described. The objective was to obtain a stable, robust, immediate release dosage form, bioequivalent to the WHO recommended comparator product, Seromycin® (cycloserine) 250 mg capsules. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. Dry granulation, based on the process feasibility and comparative results with the comparator product was selected for manufacturing of the capsules and also due to the inherent moisture sensitivity of cycloserine. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain capsules 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 (UPLC and chemical test), average weight of filled capsule, average net content of capsule, locking length of filled capsule, loss on drying, uniformity of dosage units (by weight variation), dissolution (UPLC detection), assay (UPLC), related substances (UPLC), residual solvents and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25°C/60%RH and 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage conditions in the packages proposed for marketing of the product. The product however was observed to be unstable under accelerated storage conditions due to the inherent instability of cycloserine API. 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 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 Shasun Pharmaceuticals Ltd., 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 250 mg capsules manufactured for/by Shasun Pharmaceuticals Ltd., 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 250mg)
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, 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 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/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 C_{max} values regarding cycloserine. Accordingly, the test Cycloserine 250 capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Seromycin® (The Chao Center for Industrial Pharmacy and Contract Manufacturing).

4. Summary of product safety and efficacy

[TB416 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, [TB416 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Seromycin®(The Chao Center for Industrial Pharmacy and Contract Manufacturing) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB416 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 [TB416 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB416 trade name] has been shown to be bioequivalent with Seromycin® (The Chao Center for Industrial Pharmacy and Contract Manufacturing)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB416 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 [TB416 trade name] was acceptable for the following indication: '{treatment of drug-resistant tuberculosis}', and would allow inclusion of [TB416 trade name], manufactured at Strides Pharma Science Limited , Formulation division unit II , Puducherry , 605 014 , India in the list of prequalified medicinal products.