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	[TB330 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase II/Phase III, Unit II Plot No 25–27, Survey No. 366 Premier Industrial Estate Kachigam Daman – 396 210 India
Active Pharmaceutical Ingredient(s) (API)	Cycloserine
Pharmaco-therapeutic group (ATC Code)	Drugs for the treatment of tuberculosis Antibiotics (J04AB01)
Therapeutic indication	[TB330 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*. [TB330 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

1. Introduction

[TB330 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB330 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB330 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)

D-cycloserine [(R)-4-aminoisoxazolidin-3-one], is manufactured from D-serine.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, limiting condensation products (UV-VIS), specific optical rotation, crystallinity, pH,

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

loss on drying, residue on ignition, assay (HPLC), related substances (HPLC), residual solvents, enantiomeric purity (≤ 0.5%) and heavy metals.

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.

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 materials.

Other ingredients

The capsule fill powder contains purified talc, light magnesium oxide and heavy magnesium oxide. The capsule shells contain gelatin, sodium lauryl sulphate, quinoline yellow, sunset yellow and titanium dioxide. 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 yellow/yellow size "3" hard gelatin capsule filled with white to pale yellow powder.

The capsules are packaged in plain Alu/Alu cold form laminate blisters and plain Alu/Alu strips. The capsules are stored below 25°C in the blisters/strips in the provided carton to protect the moisture sensitive and slightly hygroscopic API from hydrolysis.

[TB330 trade name] is a direct scale down in-composition of Cycloserine 250 mg capsules (TB154) of Macleods Pharmaceuticals Limited that has been prequalified previously. The two strengths are distinguished by the colour and size of the capsules. The manufacturing process includes dry mixing of the API with excipients, encapsulation and packaging. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of API and colorants, uniformity of weight and average net content of the capsule, disintegration time, loss on drying, uniformity of dosage units (by weight variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), limiting the condensation product (by UV-VIS) and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/60%RH (zone II) as long-term storage condition and for 6 months at accelerated condition (40°C/75%RH). The data showed significant degradation of the API at the accelerated storage condition 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 2004 according to internationally accepted guidelines.

A randomized, single dose, open label, non-replicate, two-period, two-treatment, two sequence crossover bioequivalence study comparing cycloserine 250 mg capsule (manufactured by Macleods Pharmaceuticals Limited India) and Seromycin capsules (Eli Lilly and company, USA) in 24+4 normal healthy male subjects in fasting condition. (Study no. WH/04/001).

The objective of the study was to compare the rate and extent of absorption of the stated cycloserine 250 mg capsules with the same dose of Seromycin® capsules (cycloserine 250 mg). The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – Cycloserine 250 mg capsule
Batch no. CD404 (Macleods Pharmaceuticals Ltd, India)

Treatment R: Reference – Seromycin® 250 mg capsule
Batch no. 6ML65M (Eli Lilly, USA)

A 12 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 15 samples within 32 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC_{inf}, AUC_{0-t}, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for cycloserine in plasma were analyzed using a validated HPLC method with fluorescence detection. The limit of quantification was stated to be 0.015 µg/mL for cycloserine.

The study was performed with 24 (+ 4 standby) participants. Data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (±SD), geometric means (AUC, C_{max}) 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)	1.35 ± 1.21	1.35 ± 1.46	–	–
C_{max} (ng/mL)	10.03 ± 2.52 (9.72)	10.55 ± 2.44 (10.26)	94.7	87.6 – 102.4
AUC_{0-t} (ng·h/mL)	159.5 ± 44.2 (154.2)	161.0 ± 43.2 (156.3)	98.6	88.8 – 109.5
AUC_{0-inf} (ng·h/mL)	228.4 ± 77.2 (216.4)	225.5 ± 92.4 (211.7)	102.2	87.1 – 119.9

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding cycloserine. Accordingly, the test product Cycloserine 250 mg capsules (Macleods Pharmaceutical Limited, India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Seromycine® 250 mg capsules (Eli Lilly, USA).

A biowaiver was granted for the additional 125 mg strength capsules (Macleods Pharmaceuticals Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Cycloserine 125 mg capsule was determined to be qualitatively the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

[TB330 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, [TB330 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Seromycine® 250 mg capsules (Eli Lilly, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB330 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 [TB330 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB330 trade name] has been shown to be bioequivalent with Seromycine® (The Chao Center for Industrial Pharmacy & Contract manufacturing).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB330 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 [TB330 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 [TB330 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II, Unit 2, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman – 396 210, India in the list of prequalified medicinal products.