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	[TB154 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceutical Limited Plot Nº 25-27, Sr. Nº 366, Premier Ind. Estate Kachigam, Daman (U.T.) India
Active Pharmaceutical Ingredient(s) (API)	Cycloserine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AB01)
Therapeutic indication	[TB154 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis. [TB154 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

1. Introduction

[TB154 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*. [TB154 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB154 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, epilepsy, psychiatric disease (e.g. depression, severe anxiety, psychosis) and in case of concurrent use of alcohol.

It is recommended that therapy is given only on the advice of a tuberculosis experienced physician.

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 is described in the USP.

The synthesis of Cycloserine was described in the drug master file of the API manufacturer and all questions of the reviewers were satisfactorily answered. The API manufacturer's specifications

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

control the synthesis and process impurities, including residual solvents, and ensure both batch-to-batch reproducibility and compliance with standard specifications.

Stress testing data demonstrated that the Cycloserine is sensitive to moisture and degradation products were included among the stability acceptance criteria.

The submitted stability studies support a six (6) months retest period, on condition that Cycloserine API is stored in tightly closed, light-resistant containers and at a temperature not exceeding 25°C.

Other ingredients

All other ingredients in the pharmaceutical product meet pharmacopoeial requirements except for the hard capsules, which are controlled according to in-house specifications.

Evidence has been provided that gelatin capsules comply with the requirements of the WHO Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products. The secondary packaging materials, LDPE bag and desiccant silica gel bag, meet compendia requirements.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The development of the final composition has been described. Dissolution profile equivalence was demonstrated against Seromycin 250 mg capsules. The compositions of the bioequivalence, dissolution, stability and validation batches were the same.

The manufacturing process of Cycloserine 250 mg Capsules includes dry mixing of the API with excipients, encapsulations and packaging. Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data were presented and assessed acceptable on three production batches.

Specifications

The specifications and associated control methods are relevant to a capsule pharmaceutical form and the manufacturing process.

Specifications and tests at release are standard and include among others limits for assay, degradation products, and dissolution.

Stability testing

Stability studies have been performed according to WHO requirements. The capsules are stable in the given packaging configuration and under all conditions. The stability results supported a shelf-life of 24 months for Cycloserine 250 mg Capsules, if they are stored in the original container and at a temperature below 25°C. Once the strips are removed from the polyethylene bag, the capsules should be used within 7 days.

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 capsule 250 mg (mfg. by Macleods Pharmaceuticals Ltd. 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 Pharmaceutical 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 h 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.

Arithmic 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

Conclusions

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 product Cycloserine 250 mg capsules (Macleods Pharmaceutical Ltd., 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).

4. Summary of product safety and efficacy

[TB154 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality

and bioavailability it is pharmaceutically and therapeutically equivalent to the reference product, Seromycine 250 mg capsules®.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[TB154 trade name] has shown to be bioequivalent with Seromycine 250 mg capsules (Eli Lilly, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB154 trade name] are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics is taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [TB154 trade name] was acceptable for the following indication: **"as a second-line antimycobacterial drug in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*"** and has advised to include [TB154 trade name], manufactured at Macleods Pharmaceutical Limited, Plot Nº 25-27, Sr. Nº 366, Premier Ind. Estate, Kachigam, Daman (U.T.) India in the list of prequalified medicinal products.