

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Cycloserine 250 mg Capsules *
Manufacturer of Prequalified Product:	Biocom JSC 54 Chapaevsky Cr 355016 Stavropol Russian Federation
Active Pharmaceutical Ingredient (API):	Cycloserine
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial (J04AB01)
Therapeutic indication:	Cycloserine 250 mg Capsules is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by <i>Mycobacterium tuberculosis</i> . Cycloserine 250mg Capsules is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Cycloserine 250 mg Capsules is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*.

Cycloserine 250 mg Capsules is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Cycloserine (reference number WHOAPI-177) 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 cycloserine, used in the manufacture of Cycloserine 250 mg Capsules, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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 specifications include tests for description, solubility, identification, condensation products, specific optical rotation, heavy metals, residue on ignition, loss on drying, pH, related substances (HPLC), assay, residual solvents, microscopic examination and microbial limits.

Other ingredients

The other core capsule ingredient is talc. The capsule shells contain gelatin, ponceau 4R (cochineal red A), quinoline yellow and titanium dioxide

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Cycloserine 250 mg Capsules are size 0 hard gelatin capsules with white body and orange cap, filled with a white or almost white powder. The capsules are packaged in an HDPE bottle with HDPE screw cap, provided with a tamper-proof ring and induction foil sealing. 1 bottle with a leaflet in a carton.

The product was designed by technology transfer of the innovator product. The product is comprised of a simple formulation of API and purified talc, filled into gelatin hard capsule shells.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three batches demonstrated the consistency of the process and the quality of the product.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (HPLC, TLC and chemical), average fill weight, uniformity of dosage units (by weight variation), dissolution, loss on drying, assay (HPLC), related substances (HPLC) and microbial limits. The test methods have been satisfactorily described and validated.

Stability testing

Stability studies have been performed at $25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$ as long-term storage condition. The data showed chemical degradation, though support the proposed shelf life and storage conditions, as well as the in-use period after first opening of the bottle, as defined in the SmPC. Excursions above 25°C should be avoided.

Conclusion

The quality part of the dossier has been accepted.

3. Assessment of Bioequivalence

The product was designed by technology transfer of the innovator product.

4. Summary of Product Safety and Efficacy

Cycloserine 250 mg Capsules has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Cycloserine 250 mg Capsules is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Seromycin[®] 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 considered. Reference is made to the SPC (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 Cycloserine 250 mg Capsules is used in accordance with the SmPC.

Efficacy and Safety

Regarding clinical efficacy and safety, Cycloserine 250 mg Capsules 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 Cycloserine 250 mg Capsules 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 to include Cycloserine 250 mg Capsules, manufactured at Biocom JSC, 54 Chapaevsky Cr, 355016 Stavropol, Russian Federation in the list of prequalified medicinal products.