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	[TB236 trade name]*
Manufacturer of Prequalified Product	Dong-A Pharmaceutical Cheon-an Plant : 404, Chaam-dong, Cheonan-city, Chungcheongnam-do, Korea
Active Pharmaceutical Ingredient(s) (API)	cycloserine
Pharmaco-therapeutic group (ATC Code)	Drugs for the treatment of tuberculosis, Antibiotics (J04AB01)
Therapeutic indication	[TB236 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis. [TB236 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

1. Introduction

[TB236 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis.

[TB236 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB236 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)

The APIMF of D-cycloserine, (R)-4-Aminoisoxazolidin-3-one, has been accepted through WHO's APIMF procedure. The API is manufactured in a few steps from D-serine. The API specifications are pharmacopoeial based and include tests for description, identification, pH, loss on drying, residual solvents, heavy metals, condensation products, residue on ignition, specific optical rotation, crystallinity, water content, related substances (HPLC) and assay. Stability testing was conducted

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

according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the didanosine is stored in the original packing material.

Other ingredients

The other core capsule ingredient is talc. The capsule shells contain FD&C Red #3/erythrosine, FD&C Yellow #6/sunset yellow FCF, gelatin, sodium lauryl sulfate and titanium dioxide.

Finished pharmaceutical product (FPP)

[TB236 trade name] are hard gelatin capsules, with pink-coloured cap and white-coloured body, filled with a white to slightly yellowish powder. The capsules are presented in aluminium-aluminium blister cards.

Specifications

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

Pharmaceutical development and manufacture

The multisource [TB236 trade name] is similar in core capsule composition to that of the comparator product Seromycin® and contains talc as the only excipient. The manufacturing process entails mixing of the API with talc, encapsulation and packaging. The capsules are packaged in aluminium-aluminium blisters cards to protect the API, which hydrolysis easily, from excessive moisture. Similar to the comparator product, the multisource product showed very rapidly dissolution properties in the three BCS media. Validation data presented for three batches demonstrated the consistency of the process and the quality of the product. Satisfactory in-process controls have been established.

Stability testing

Stability studies have been performed on several batches, including the three batches used in the process validation studies, at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage condition and for six months at accelerated conditions. The data showed degradation of the API, more pronounced at accelerated storage conditions, though all attributes were within the agreed specifications at all storage conditions. Excursions above 30°C should be limited. 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 2010 according to internationally accepted guidelines.

An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose, evaluation of relative oral bioavailability of cycloserine capsules 250 mg of Dong-A Pharmaceutical co. Limited, Korea with that of 'Seromycin®' (cycloserine) 250 mg capsules of the Chao Center for Industrial Pharmacy & Contract manufacturing, USA, in healthy adult male subjects under fasting condition (study no. BA10508106-01).

The objective of the study was to compare the bioavailability of the stated Cycloserine 250 mg capsule manufactured by Dong-A Pharmaceutical Co., Ltd., Chean-an, Korea (test drug) with the same dose of the reference formulation (Seromycin®, Lilly) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 capsule Cycloserine 250 mg (cycloserine 250 mg) Batch no. 0378

Treatment R: Reference – 1 capsule Seromycin® (cycloserine 250 mg) Batch no. 10E0018P

A 18 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 200 ng/ml for cycloserine.

The study was performed with 28 participants; data generated from a total of 26 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 tables:

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)	1.06 ± 0.75	0.93 ± 0.65	–	–
C_{max} (µg/mL)	11.9 ± 2.0 (11.7)	12.6 ± 2.2 (12.4)	94.6	88.8 – 100.8
AUC_{0-t} (µg·h/mL)	177 ± 40 (172)	183 ± 40 (179)	96.2	93.2 – 99.3
AUC_{0-inf} (µg·h/mL)	203 ± 54 –	213 ± 55 –	–	–

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 capsule Cycloserine 250 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Seromycin® (Lilly).

4. Summary of product safety and efficacy

[TB236 trade name] 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 [TB236 trade name] 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 taken into account. Reference is made 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 [TB236 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB236 trade name] has shown to be bioequivalent with Seromycin®, Lilly, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB236 trade name] 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 [TB236 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 has advised that the quality, efficacy and safety of [TB236 trade name] allow inclusion of [TB236 trade name], manufactured at Dong-A Pharmaceutical, Cheon-an Plant 404, Chaam-dong, Cheonan-city, Chungcheongnam-do, Korea, in the list of prequalified medicinal products.