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	[TB385 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Area, Chikalthana Aurangabad 431210 India
Active Pharmaceutical Ingredient(s) (API)	Cycloserine
Pharmaco-therapeutic group (ATC Code)	Drugs for the treatment of tuberculosis, Antibiotics (J04AB01)
Therapeutic indication	[TB385 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB385 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed

1. Introduction

[TB385 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB385 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

[TB385 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)

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 [TB385 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

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

(APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the capsule fill formulation include glyceryl behenate, microcrystalline cellulose and calcium carbonate. The capsule shell contains gelatin, FD& C blue #1/brilliant blue FCF, erythrosine, titanium dioxide, FD& C yellow #6/sunset yellow FCF, FD& C yellow #5/ tartrazine, methyl paraben and propyl paraben while the printing ink contains shellac, polysorbate, propylene glycol, ponceau 4R and red iron oxide. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[TB385 trade name] are size '1 ' hard gelatin capsules with blue coloured cap imprinted with 'Lupin' logo in white colour and yellow coloured body imprinted with 'LUPIN' in red ink. The capsules, filled with white to pale pink granular powder, are packaged in plain aluminium/cold forming aluminium-aluminium blister cards.

The development of the final composition of the capsules has been described. The objective was to develop a solid oral dosage form, bioequivalent to the WHO recommended comparator product, CycloSERINE capsules USP 250 mg (Purdue GMP Centre, US). The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility data. Since the API is very sensitive to temperature and moisture, glyceryl behenate, a hydrophobic diluent, and calcium carbonate, an alkalizer, were included to improve the bulk density and remove voids in capsule filling; furthermore, dry granulation by mixing and compaction process followed by blending, drying, lubrication and capsule filling was selected for manufacturing of the finished pharmaceutical product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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 are pharmacopoeial based and include tests for description, identification of the API (HPLC and chemical reaction), average weight, average filled content of capsule, uniformity of dosage units (by weight variation and content uniformity), loss on drying, dissolution (HPLC detection), assay (HPLC), related substances (HPLC), condensation product and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25°C/60%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data showed significant degradation of the API at the accelerated storage condition and indicated some degradation at the long-term storage conditions, though remaining within agreed limits. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study comparing Cycloserine capsules 250 mg manufactured by Lupin Limited, India, with CycloSERINE (cycloserine capsules, USP) 250 mg manufactured by Purdue GMP Centre, West Lafayette, IN 47906, USA in healthy, adult, human subjects under fasting conditions (study no. LBC-19-141).

The objective of the study was to compare the bioavailability of the stated Cycloserine 250 mg capsule manufactured by/for Lupin Limited, India (test drug) with the reference formulation CycloSERINE (Purdue GMP Centre) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy 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. A990028.

Treatment R: Reference – 1 capsule CycloSERINE 250 mg (cycloserine 250 mg) Batch no. 18N0034P.

A 10 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 5 ng/ml for cycloserine.

The study was performed with 36 participants; data generated from a total of 33 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.74 ± 0.36	1.21 ± 0.67	-	-
C_{max} (µg/ml)	10.2 ± 2.2 (10.1)	10.5 ± 2.7 (10.0)	100.8	93.9 – 108.2
AUC_{0-t} (µg.h/ml)	175 ± 36 (170)	185 ± 42 (179)	94.9	92.0 – 98.0
AUC_{0-inf} (µg.h/ml)	184 ± 42 --	195 ± 49 --	-	-

*geometric mean

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

4. Summary of product safety and efficacy

[TB385 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, [TB385 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product CycloSERINE, for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB385 trade name] is considered acceptable when guidance and restrictions as stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.Benefit risk assessment and overall conclusion.

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 [TB385 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB385 trade name] has been shown to be bioequivalent with CycloSERINE 250 mg tablet (Purdue GMP Centre, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB385 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 [TB385 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 [TB385 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Aurangabad 431210, India in the list of prequalified medicinal products.