

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:	Terizidone 250mg Capsules ¹
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Unit II, Plot No. 25 – 27, Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210 India Tel: +91-260-2240125 Fax: +91-260-2241565
Active Pharmaceutical Ingredient (API):	Terizidone
Pharmaco-therapeutic group (ATC Code):	Drugs for the treatment of tuberculosis, Other drugs for treatment of tuberculosis (J04AK03)
Therapeutic indication:	Terizidone Capsules 250 mg is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by <i>Mycobacterium tuberculosis</i> . Terizidone Capsules 250 mg is only indicated as a second -line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

¹Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

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

Terizidone Capsules 250 mg is only indicated as a second -line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

Terizidone 250mg Capsules 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)

Terizidone is a slightly hygroscopic white to yellowish white coloured powder. It is manufactured from terephthalaldehyde and D-cycloserine. The R-configuration of the chiral C-atom of D-cycloserine is conserved in the synthesis, thus terizidone has the R,R-configuration. The other isomers are controlled in the API specifications. Terizidone is of BCS low solubility. It shows polymorphism and only one polymorphic form is consistently produced.

The API specifications include tests for description, solubility, identification (IR, UV), loss on drying, water content (KF), heavy metals, residue on ignition, related substances (HPLC, TLC), terephthalaldehyde and cycloserine content (UV), sum of terizidone diastereomer and enantiomer content (HPLC; $\leq 0.2\%$) assay (titrimetric), residual solvents (GC), particle size distribution and polymorphic form (XRPD).

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 packaging.

Other ingredients

The capsule fill powder contains microcrystalline cellulose, disodium edetate, hypromellose and stearic acid. The capsule shells contain gelatin, sodium methyl paraben, sodium propyl paraben, sodium lauryl sulphate, titanium dioxide, brilliant blue and carmoisine. A CEP was submitted for gelatin used in the manufacture the capsule shells. It meets the EU criteria for products with risk of transmitting animal spongiform encephalopathies. Attestation that all of the other excipients are free from TSE/BSE has been provided by the suppliers of the raw materials.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a blue colour cap and blue colour body size "0" hard gelatin capsule containing creamy coloured granular powder. The capsules are packaged in aluminium-aluminium strips and in HDPE bottles with polypropylene screw caps.

The aim was to develop a stable and robust formulation of an immediate release capsule dosage form that would be bioequivalent to the WHO comparator product, Terivalidin Capsules 250 mg. The selection of the excipients was based on their compatibility with terizidone and on their suitability to achieve the desired characteristics of the formulation. The API exhibit very poor flow properties. Thus a non-aqueous granulation process was selected to get the desired flow properties for filling of the capsule shells. Satisfactory in-process controls have been established.

Product specifications

The product specifications include tests for description, identification of the API (HPLC, UV) and colourants in the capsule shell, average net content (mg), uniformity of dosage units (by weight variation), disintegration time, loss on drying, dissolution (HPLC detection), cycloserine content (UV), related substances (HPLC), residual solvents (GC), assay (HPLC), and microbial limits.

Stability testing

Stability studies have been conducted on samples stored at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for 6 months at accelerated condition (40°C/75%RH) in the packaging proposed for marketing of the product. The data showed an increase in loss on drying, cycloserine content and other degradation products. Failures were seen at the accelerated storage condition and after 24 months at the zone IVb storage condition. Excursions above 30°C should thus be avoided 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 2014 according to internationally accepted guidelines.

Study title: Bioequivalence study of single dose of Terizidone capsules 250 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Terivalidin[®] (terizidone) capsules 250 mg manufactured by Sanofi Aventis, South Africa in healthy, adult, human subjects under fasting condition (study no. BEQ-1290-TERI-2014).

The objective of the study was to compare the bioavailability of the stated Terizidone 250 mg capsules manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Terivalidin[®] (Sanofi Aventis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

- Treatment T: Test – 1 capsule Terizidone 250 mg
(terizidone 250 mg)
Batch no. ETA4402C
- Treatment R: Reference – 1 capsule Terivalidin[®]
(terizidone 250 mg)
Batch no. 2G236A

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 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 the metabolite cycloserine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 202 ng/ml for cycloserine.

The study was performed with 24 participants; data generated from a total of 22 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 \pm SD (*)	Reference (R) arithmetic mean \pm SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.84 \pm 0.89	1.96 \pm 0.75	-	-
C_{max} (μ g/ml)	6.84 \pm 1.42 (6.71)	5.93 \pm 0.79 (5.91)	113.6	108.5 – 118.9
AUC _{0-t} (μ g.h/ml)	140 \pm 25 (137)	128 \pm 26 (126)	109.3	102.9 – 116.1
AUC _{0-inf} (μ g.h/ml)	154 \pm 26 (152)	139 \pm 25 (137)	111.5	106.4 – 116.8

* geometric mean

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 Terizidone 250 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Terivalidin[®] (Sanofi Aventis).

4. Summary of Product Safety and Efficacy

Terizidone 250mg Capsules mg 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 Terizidone 250mg Capsules is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Terivalidin[®] 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 Terizidone 250mg Capsules is used in accordance with the SmPC.

Bioequivalence

Terizidone 250mg Capsules has shown to be bioequivalent with Terivalidin[®] (Sanofi Aventis).

Efficacy and Safety

Regarding clinical efficacy and safety, Terizidone 250mg 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 Terizidone 250mg 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 use of first line drugs is not appropriate due to resistance or intolerance”** and has advised that the quality, efficacy and safety of Terizidone 250mg Capsules allow inclusion of Terizidone 250mg Capsules, manufactured at Macleods Pharmaceuticals Limited, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210 India, in the list of prequalified medicinal products.