Notes on the Design of Bioequivalence Study:
Terizidone

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release products containing terizidone.

Pharmacokinetics of terizidone

Terizidone pharmacokinetic properties are poorly described in the literature, mainly because terizidone was developed in the 1970s, when bioanalytical methods were limited. In these studies, terizidone was not measured, but estimated, based on its active metabolite cycloserine using a colorimetric method. Therefore, it was not known if terizidone itself is systemically available.

According to the information currently available to WHO PQT/MED, terizidone is not measurable in plasma and consequently it seems to be hydrolyzed completely into cycloserine pre-systemically.

Guidance for the design of bioequivalence studies

Taking into account the pre-systemic clearance of terizidone, the following guidance with regard to the study design should be taken into account.

Design: A single-dose cross-over design is recommended.

Dose: The 250 mg capsule strength is invited so a dose of 1 x 250 mg should be employed in a BE study.

Fasted/fed: The bioequivalence study should be conducted in the fasting state as terizidone can be taken irrespective of meals.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product, however, as the parent is not measurable, the active metabolite cycloserine should be used to assess bioequivalence.

Sample size: Cycloserine pharmacokinetic parameters, C_{max} and AUC_{0-t}, after the administration of terizidone in the fasting state, seem to possess low variability (8–13%) based on information available to the PQT/MED. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of cycloserine after terizidone administration of approximately 17 hours (range: 10 – 24 hours), a washout period of 7 − 14 days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first four hours after administration to properly characterize the C_{max} of cycloserine. It is not necessary to take blood samples beyond 72 hours for the characterization of cycloserine pharmacokinetics.

Analytical considerations: Terizidone is not detected in plasma with a bioanalytical method with a LLOQ of 0.2 μg/ml. Therefore, bioequivalence should be based on the determination of its active metabolite cycloserine. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the Cmax in most profiles of each formulation (test or comparator).

Statistical considerations: The data for cycloserine should meet the following bioequivalence standards in a single-dose cross-over design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to comparator product should be within 80.00 – 125.00%

- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.