Notes on the Design of Bioequivalence Study: Terizidone

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team: medicines (PQTm) 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.


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, and using a colorimetric method. Therefore, it was not known if terizidone itself is systemically available.

According to the information currently available to WHO PQTm, 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.

Dose: As terizidone is not highly soluble in the whole physiological pH range, the maximum proposed strength (i.e., 300 mg for the 250 mg and 300 mg strengths) should be employed in the bioequivalence study.

Fasting/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 utilized. It is not necessary to include patients in the bioequivalence study.

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.

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 a information available to the PQTm. These data will 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 $C_{\text{max}}$ of cycloserine. It is not necessary to take blood samples beyond 72 hours for the characterization of cycloserine pharmacokinetics.

**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 will be used to assess bioequivalence.

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

- The 90% confidence interval of the relative mean $\text{AUC}_{0-t}$ of the test to reference product should be within 80–125%
- The 90% confidence interval of the relative mean $C_{\text{max}}$ of the test to reference product should be within 80–125%.