Notes on the Design of Bioequivalence Study: Linezolid

Notes on the design of bioequivalence studies with products invited to be submitted 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 linezolid.

Pharmacokinetics of linezolid

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing. Absolute oral bioavailability of linezolid (oral and intravenous dosing in a crossover study) is complete (approximately 100%). Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets. Linezolid may be taken with or without food. The elimination half-life of linezolid averages at about 5-7 hours. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations, however, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of linezolid the following guidance with regard to the study design should be taken into account:

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes linezolid 150 mg dispersible tablets, linezolid 600 mg tablet, and linezolid 20 mg/ml powder for oral suspension, the bioequivalence study should be conducted with these strengths at the 600 mg dose level.

The bioequivalence study for the tablet and the powder for oral suspension could be waived according to the requirements for Biopharmaceutics Classification System (BCS) biowaivers since linezolid is classified as BCS class I drug. However, for the dispersible tablet the BCS biowaiver is not possible since the comparator product is a tablet.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g. a tablet that should be taken with a glass of water, and a dispersible tablet to be dispersed in 10 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions.
**Fasting/fed:** The bioequivalence study should be conducted in the fasted state.

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

**Sample size:** Information currently available to PQTM indicates that the intra-subject variability for linezolid $C_{\text{max}}$ is around 12%. These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

**Washout:** Taking into account the elimination half-life of linezolid in healthy volunteers of 7 hours, a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive for the first hours after administration to properly characterize the $C_{\text{max}}$ of linezolid. Sampling times beyond 36 hours are not necessary for the quantification of linezolid. For example, blood samples might be taken at predose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 6.00, 8.00, 12.00, 16.00 and 24.00 and 36.00 hours after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure linezolid in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{\text{max}}$ in most profiles of each formulation (test or comparator).

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the biopharmaceutical quality of the product. The disposition of linezolid should be characterized and the determination of bioequivalence will be based on the parent compound.

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

- The 90% confidence interval of the relative mean $AUC_{0-t}$ 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%.