Notes on the Design of Bioequivalence Study:
Oseltamivir

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 oseltamivir.

Pharmacokinetics of oseltamivir

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5% relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to oseltamivir carboxylate with a half-life of 1.5 h. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of oseltamivir, 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 30 mg, 45 mg and 75 mg capsules, the highest recommended therapeutic strength should be employed in the bioequivalence study. For the 6 mg/ml and 12 mg/ml powder for oral suspension included in the EoI, the highest recommended therapeutic dose of 75 mg should be employed in the bioequivalence study.

Oseltamivir is a compound with limited absorption, but the available data on solubility does not allow its BCS classification. If the Applicant generates the solubility data and stability data in the physiological pH range and classifies the drug according to the BCS criteria as highly soluble, oseltamivir could be classified as BCS class III drug and a BCS biowaiver could be applicable.

The suspension may be biowaived if the same amount of sorbitol is used as in the reference product and if the API in the powder for suspension can be proved to be completely in solution at the time of administration.
**Fasting/fed:** As the comparator product can be taken with or without meals, bioequivalence should be investigated in fasted state.

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

**Sample size:** Oseltamivir Cmax in the fasting state seems to possess moderate – high variability (27 - 37%). In contrast AUC₀₋ₜ variability is low – moderate (9 – 25%). These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** At least 7 days.

**Blood sampling:** For example: predose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 5.00, 6.00, 8.00, 10.00 and 12.00 h after drug administration for the characterisation of oseltamivir parent drug.

**Analytical considerations:** Information currently available indicates that it is possible to measure oseltamivir in human plasma using LC-MS/MS analytical methodology. 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).

**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 oseltamivir should be characterized and the determination of bioequivalence will be based on the parent compounds.

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

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

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

Information currently available to the PQTm suggests that the comparator product might be a highly variable drug product for $\text{C}_{\text{max}}$, but not for $\text{AUC}_{0\text{t}}$. Widening of the acceptance range for $\text{C}_{\text{max}}$ might be acceptable if the applicant conducts a replicate cross-over study to estimate variability of the comparator product more accurately and the high variability of $\text{C}_{\text{max}}$ is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 6, TRS 1003.