Notes on the Design of Bioequivalence Study: Zanamivir

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 pre-dispensed inhalation powder containing zanamivir.

**Pharmacokinetics of zanamivir**

The absolute oral bioavailability of zanamivir is low, averaging 2% (range 1 to 5 %). After oral inhaled administration, a median of 10 to 20% of the dose was systemically absorbed, with maximum serum concentrations (47 mcg/ml) generally reached after 0.75 hours (0.08 – 2 hours). The mean serum half-life of 3.56 – 5.05 h ranges between 2.23 and 9.49 hours, suggesting that the elimination rate is limited by absorption. Approximately 90% of zanamivir was excreted unchanged in the urine. The kinetics of inhaled zanamivir were linear, as suggested by the dose proportionality.

**Guidance for the design of bioequivalence studies**

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

**Design:** Two cross-over designs are recommended. A single dose study without active charcoal blockade to compare systemic exposure as measurement of systemic safety, and a single dose study with active charcoal blockade to assess pulmonary deposition as measurement of efficacy. It should be demonstrated previously that oral absorption of the swallowed fraction is blocked by the administration protocol of active charcoal.

**Dose:** As the EoI includes only the 5 mg/dose, a therapeutic dose of 2 x 5 mg should be administered in the bioequivalence studies to obtained measurable levels.

**Fasting/fed:** As this product is administered by pulmonary route, bioequivalence should be investigated in fasted state.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence studies.
**Sample size:** There is no bioequivalence data available on Zanamivir to estimate the intra-subject variability of \( C_{\text{max}} \) and AUC. Therefore, pilot studies should be conducted to design the pivotal studies. The intra-subject variability is highly dependent on the consistency and correctness of the inhalation maneuvers. Therefore, the bioequivalence studies should be conducted in centers experienced with inhalation products to ensure that participants are trained adequately and the subjects with inadequate inhalation maneuvers are excluded.

**Washout:** At least 7 days.

**Blood sampling:** For example: predose, 0,03, 0.08, 0.17, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 18.00 and 24.00 h after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure zanamivir in human serum 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. In addition, zanamivir is not metabolised. The disposition of zanamivir should be characterized and the determination of bioequivalence will be based on the parent compound.

**Statistical considerations:** The data for zanamivir should meet the following bioequivalence standards in both single-dose, crossover design studies:

- 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%.

Information currently available to the PQTm suggests that inhalation products are frequently highly variable drug products for \( C_{\text{max}} \) due to the variability in the inhalation maneuvers. Widening of the acceptance range for \( C_{\text{max}} \) 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 \( C_{\text{max}} \) is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 6, TRS 1003.