Notes on the Design of Bioequivalence Study: Oseltamivir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (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-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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 single-dose 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.

A biowaiver for the suspension may be possible if the same amount of sorbitol is used as in the reference product and if the API in the powder for suspension can be proven to be completely in solution at the time of administration.

Fasted/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 recruited. It is not necessary to include patients in the bioequivalence study.

Parent or metabolite data for assessment of bioequivalence: Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug). Following absorption, the prodrug is rapidly converted to oseltamivir. Therefore, bioequivalence should be based on the determination of oseltamivir.

Sample size: Oseltamivir C_{max} in the fasting state seems to exhibit moderate – high variability (27 - 37%). In contrast, AUC_{0-t} variability is low – moderate (9 – 25%). These data may facilitate the calculation of a sufficient sample size for the single-dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of oseltamivir (10 hours), a washout phase of at least 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling for oseltamivir should be intensive the first four hours after administration to properly characterize the C_{max} of oseltamivir. It is not necessary to take blood samples beyond 12 hours for the characterization of oseltamivir pharmacokinetics. For example, samples may be taken at pre-dose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 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.

Analytical considerations: Information currently available to PQT/MED 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 C_{max} in most profiles of each formulation (test or comparator).

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

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of C_{max} or AUC_{0-t} is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of C_{max} and/or AUC_{0-t}. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and WHO guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.

A BCS- based biowaiver for oseltamivir suspension is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the ICH Guideline "*Biopharmaceutics Classification System-Based Biowaivers*" M9 (2019) and the PQT/MED guidance "*PQT/MED-specific Annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications*" (2021).