Notes on the Design of Bioequivalence Study: Buprenorphine

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited sublingual tablets containing buprenorphine.

Pharmacokinetics of buprenorphine

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The bioavailability of buprenorphine by the oral route is only 14% and, therefore, the sublingual route is preferred. Peak plasma concentrations are achieved 90 minutes after sublingual administration with a shorter t_{max} when a higher dose is administered (median t_{max} of 0.75 h for the 16 mg strength, 1.00 h for the 12 mg strength, 1.02 h for the 8 mg strength and 1.5 h for the 2 mg strength). Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 20 to 26 hours (range 9 – 69 h), due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.

Mean dose-normalised C_{max} and AUC values appeared not to change with dose, indicating approximate dose-proportional increases of these parameters across the 8 – 16 mg doses

Guidance for the design of bioequivalence studies

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

Design: A single-dose, crossover design is recommended.

Dose: As the EoI includes 0.2 mg, 0.4 mg, 2 mg, 4 mg, 8 mg sublingual tablets, the highest strength should be tested. The requirement to conduct BE studies with the lower strengths can be waived if the conditions for the additional strength biowaiver are met.

Fasted/fed: As the comparator product can be taken with or without food since relevant absorption is sublingual, a fasted state study is recommended. Tablets should be placed under the tongue until they are dissolved; swallowing the tablets reduces the bioavailability of the drug.

Subjects: Healthy adult subjects should be used. It is not necessary to include patients in the bioequivalence study. A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of buprenorphine. Norbuprenorphine data should be submitted as supportive evidence.

Sample size: Information currently available to the PQT/MED indicates that the intra-subject variability for buprenorphine C_{max} is around 23% and 12 – 14% for AUC. These data will facilitate the calculation of sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of methadone in healthy volunteers (25 hours), a washout period of one week or 10 days is considered sufficient to prevent carry over.

Blood sampling: As buprenorphine t_{max} can range between 0.5 h and 3.0 h, blood sampling should be intensive the first hours after administration to cover the peak of buprenorphine, e.g., pre-dose and at 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, 4.50, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post dose. It is not necessary to take blood samples over a longer time period, as this will only substantiate the elimination phase of buprenorphine.

Analytical method: Information currently available to the PQT/MED indicates that it is possible to measure buprenorphine in human plasma using LC-MS/MS analytical methodology (LLOQ of 0.05 ng/ml). 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for buprenorphine should meet the following bioequivalence standards in a single dose cross-over 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_{max} of the test to reference product should be within 80-125%.