Notes on the Design of Bioequivalence Study: Atazanavir + Ritonavir

Notes on the design of bioequivalence studies are issued to advise applicants on how to plan and conduct such studies with products invited for submission to the WHO Prequalification Team: medicines (PQT). Deviations from the approach outlined below are acceptable where justified by sound scientific evidence.


Below, additional specific guidance is provided on the invited fixed dose combination products containing atazanavir and ritonavir.

**Pharmacokinetics of atazanavir**

After oral administration, atazanavir peak plasma concentrations are reached after approximately 2–3 hours. Concomitant administration of atazanavir sulfate with a light meal or a high fat meal enhances the relative bioavailability of atazanavir by approximately 70% and 35%, respectively. Co-administration of food significantly also reduces the observed pharmacokinetic variability of atazanavir. Consequently, atazanavir is to be taken with food.

Atazanavir is extensively metabolized, primarily through monooxygenation and dioxygenation pathways. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in the AUC (area under the curve) and Cmax values over the dose range of 200–800 mg once daily.

**Pharmacokinetics of ritonavir**

After oral administration, ritonavir peak plasma concentrations are observed after approximately 4 hours. Concomitant administration of ritonavir with food improves absorption relative to the fasted state. Ritonavir should preferably be administered with food.

Ritonavir is metabolized by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolized by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir. Ritonavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC.
Guidance for the design of bioequivalence studies

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

**Dose:** Due to the non-linearity of the pharmacokinetics of the active ingredients, the highest recommended therapeutic dose for the combination product should be employed in the bioequivalence study.

**Fasting/fed:** As it is recommended to take the originator monocomponent tablets with food, and the absorption is more variable if the tablets are taken in the fasted state, we recommend administration of the tablets with a standard breakfast, not a high-fat, high-calorie meal, as a standard breakfast is considered to be closest to real life conditions in patients.

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

**Analytical considerations:** The disposition of both atazanavir and ritonavir should be characterized and the determination of bioequivalence will be based on both parent compounds.

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

- The 90% confidence interval of the relative mean AUC of the test to reference product should be within 80–125%

- The 90% confidence interval of the relative mean Cmax of the test to reference product should be within 80–125%.