EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Question & answer on the need for bioequivalence studies with acid reducing agents (ARAs)

Question

When is an additional bioequivalence study with concomitant treatment with an acid-reducing agent needed to show bioequivalence in the cases where a generic product uses another salt/API form or different pH modifying excipient/technology than the reference product?

Response

The absorption of active substances with pH-dependent solubility may be altered by the gastric pH. Therefore, there are products for which bioequivalence under normal fasting conditions may not ensure bioequivalence in a gastric pH-altered situation. This is the case for those products where the excipients affect the pH of gastric fluids, or where differences in the salt form, hydration/solvation state or polymorphism change the pH-solubility profile of the active substance, e.g., in the presence of an acid-reducing agent or achlorhydria.

To date, EMA product-specific bioequivalence guidelines have been published referencing to the salt, polymorphic form and hydration/solvation state of the drug substance used in the formulation of the reference medicinal product with its specific biopharmaceutical characteristics. Therefore, even if a published product-specific bioequivalence guideline does not explicitly highlight this, an additional bioequivalence study with concomitant treatment of a Proton-Pump Inhibitor (PPI) as an acid-reducing agent is necessary in principle to demonstrate bioequivalence if all of the following conditions are met:

a) The products under comparison contain an active substance with pH-dependent solubility in the range between pH 1.2 and 6.8, as described in ICH M9 as equilibrium solubility; and:

b) There are qualitative or quantitative differences in the pH-modifying excipient(s), significant differences in manufacturing process affecting the pH-dependent dissolution or differences in the salt, hydration/solvation state or polymorphic form with a different pH-dependent solubility.

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This additional study should be conducted under conditions of pre-treatment with a PPI for 4 days to ensure maximum effect. In principle this study should be conducted in fasted state, except if the reference medicinal product is administered only in the fed state.

However, this study may be waived with a clinical justification demonstrating that these products are not expected to be taken with acid-reducing agents or prescribed to patients who may suffer from achlorhydria.

If concomitant use is anticipated, then a PPI study may still be waived if it can be demonstrated that bioequivalence in a gastric pH-altered situation can be expected. Such a justification should be based on a comprehensive consideration of:

a) The pH-solubility profile of the active substance in the salt / hydration / solvation state / polymorphic form of the products under comparison in the pH range from 1.2 to 6.8 (e.g., a waiver may be acceptable if both forms are highly soluble according to the Biopharmaceutics Classification System).

b) Effect of the PPI on the absorption of active substance from the reference medicinal product.

c) Excipient composition and the manufacturing process affecting the pH-dependent dissolution in the case of formulations designed to avoid the impact of the pH on drug absorption.

d) *In vitro* dissolution profiles.

Modelling, e.g., appropriately validated/qualified PBPK modelling or semi-mechanistic absorption models may be used to further assess the risk of lack of bioequivalence.

For example, if the pH-solubility profile is similar and no pH-modifying excipients or special technologies are used, the study could be waived. Similarly, if it is known that PPIs do not affect the absorption of the API form employed in the reference medicinal product and the new form of the active substance exhibits a higher solubility, the study could be waived. In contrast, if:

- it is known that the reference medicinal product is affected by PPIs, or
- it was developed to avoid the effect of PPIs, or
- the applied form of the active substance exhibits a lower solubility, even if not detected in the corresponding in vitro dissolution profiles, and
- the lack of relevance cannot be justified by reference to other data (e.g., literature or modelling),

then an additional study with concomitant treatment of a PPI is necessary.

Decision Tree