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Committee for Medicinal Products for Human Use (CHMP)

Prasugrel hydrochloride film-coated tablets 5 mg and 10 mg product-specific bioequivalence guidance

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[†]This revision concerns the addition of 'hydrochloride' to the title and the section on BCS classification and the addition of an 'additional study under conditions of elevated gastric pH' and 'other information' to the section on bioequivalence study design



Keywords	<i>Bioequivalence, generics, prasugrel</i>
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Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two</p> <p>Background: Prasugrel hydrochloride may be considered a low solubility compound.</p>
<p>Bioequivalence study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p> <p>An additional study under conditions of elevated gastric pH, i.e. fed or after multiple day pre-treatment with a proton pump inhibitor (PPI) such as pantoprazole (40 mg b.i.d. for 4 days) is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel, unless scientifically justified i.e. considering solubility, dissolution profiles and formulation.</p>

	<p>Background: Elevated gastric pH affects the bioavailability of prasugrel differently in different pharmaceutical forms.</p>
	<p>Strength: 10 mg</p> <p>Background: Highest strength to be used for a drug with linear pharmacokinetics and low solubility.</p>
	<p>Number of studies: One single dose study unless an additional study under conditions of elevated gastric pH is needed for a different salt form than the originator or the free base of prasugrel</p>
	<p>Other information: It should be justified/demonstrated that the conversion from prasugrel salt to free base is not more than 70%.</p>
Analyte	<p><input type="checkbox"/> parent <input checked="" type="checkbox"/> metabolite <input type="checkbox"/> both</p> <p>Background: The parent compound is not detected in human or animal plasma (or other biological matrix). Bioequivalence should be based on the first metabolite, R-95913.</p>
	<p><input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine</p>
	<p>Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no</p>
Bioequivalence assessment	<p>Main pharmacokinetic variables: AUC_{0-t} and C_{max}</p>
	<p>90% confidence interval: 80.00 – 125.00%</p>

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max} . If high intra-individual variability ($CV_{intra} > 30\%$) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether in vivo studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III). The Applicant may choose between two options: in vivo approach or in vitro approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).