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Committee for Medicinal Products for Human Use (CHMP)

Dabigatran etexilate hard capsule 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	October 2016
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Agreed by Pharmacokinetics Working Party	April 2018
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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)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Dabigatran etexilate may be considered a low solubility compound with limited absorption.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** An additional study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI), such as pantoprazole (40 mg b.i.d. for 4 days), should be conducted in addition to the regular study under fasting conditions. **Background:** Solubility of dabigatran etexilate is pH dependent. PPIs may affect the bioavailability of dabigatran differently depending on the formulation.

	Strength: 150 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: Two single dose studies (fasting and under conditions of pre-treatment with a PPI).
Analyte	☐ **parent** ☒ **metabolite** ☐ **both** **Background:** Dabigatran etexilate is a prodrug. After oral administration it is rapidly and completely converted to dabigatran, which is the active form in plasma.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00 – 125.00%

* 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 Cmax. If high intra-individual variability (CVintra > 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).