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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

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| **Draft agreed by Pharmacokinetics Working Party** | October 2016 |
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* This revision addresses textual amendments in accordance with the ICH M13A guideline


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| **Keywords** | ***Bioequivalence, generics, dabigatran*** |



**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union



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

*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)*

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| **BCS Classification**** | **BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two**<br>**Background:** Dabigatran etexilate mesilate may be considered a low solubility compound with limited absorption. |
| **Bioequivalence study design**<br>*in case a BCS biowaiver is not feasible or applied* | **single dose**<br>**cross-over** |
| | **healthy volunteers** |
| | ☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**<br>An additional study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI) should be conducted in addition to the regular study under fasting conditions. |

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| | A waiver for this PPI study may be applicable if it can be shown that the products are manufactured using the same technology and if excipients that might modify gastric pH are qualitatively the same and quantitatively similar between test and reference product.<br><br>**Background:** Solubility of dabigatran etexilate mesilate is pH dependent. PPIs may affect the bioavailability of dabigatran differently depending on the formulation. |
| | **Strength:** 150 mg<br>**Background:** Highest strength to be used for a drug with linear pharmacokinetics. |
| | **Number of studies:** Two single dose studies (fasting and under conditions of pre-treatment with a PPI). |
| **Analyte** | ☐ **parent** ☒ **metabolite** ☐ **both**<br>**Background:** Dabigatran etexilate mesilate 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 seem 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).