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Committee for Medicinal Products for Human Use (CHMP)

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

Draft

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| Draft agreed by Pharmacokinetics Working Party | October 2016 |
| Adopted by CHMP for release for consultation | 15 December 2016 |
| Start of public consultation | 22 December 2016 |
| End of consultation (deadline for comments) | 31 March 2017 |

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu


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|---|---|
| **Keywords** | ***Bioequivalence, generics, dabigatran etexilate*** |



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# Dabigatran etexilate, hard capsules, 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 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** |
| | **Strength:** 150 mg<br>**Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility. |

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| **Analyte** | ☐ **parent** ☒ **metabolite** ☐ **both**<br>**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 $C_{max}$. 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).