



1 15 December 2016
2 EMA/CHMP/805498/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Dabigatran etexilate, hard capsules, 75 mg, 110 mg and**
5 **150 mg product-specific bioequivalence guidance**
6 **Draft**

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

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Comments should be provided using this [template](#). The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

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Keywords	<i>Bioequivalence, generics, dabigatran etexilate</i>
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12 Dabigatran etexilate, hard capsules, 75 mg, 110 mg and 150 mg product-specific
 13 bioequivalence guidance

14 Disclaimer:

15 *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*
 16 *marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

17 Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two Background: Dabigatran etexilate may be considered a low solubility compound with limited absorption.
Bioequivalence study design <i>in case a BCS biowaiver is not feasible or applied</i>	single dose cross-over healthy volunteers <input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed Strength: 150 mg Background: highest strength to be used for a drug with linear pharmacokinetics and low solubility.

Analyte	<input type="checkbox"/> parent <input checked="" type="checkbox"/> metabolite <input type="checkbox"/> 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.
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} and C _{max}
	90% confidence interval: 80.00–125.00%

18 * As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to
19 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-
20 individual variability (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.

21 ** 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
22 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
23 case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility
24 experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being
25 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
26 unacceptable differences in the excipient composition).