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3 Committee for Medicinal Products for Human Use (CHMP)

4 Rivaroxaban film-coated tablets 2.5, 10, 15 and 20mg 5 product-specific bioequivalence guidance

6 Draft

Draft Agreed by Pharmacokinetics Working Party	July 2015
Adoption by CHMP for release for consultation	24 September 2015
Start of public consultation	1 October 2015
End of consultation (deadline for comments)	1 January 2016

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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	***Bioequivalence, generics, rivaroxaban***

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Rivaroxaban film-coated tablets 2.5, 10, 15 and 20mg 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)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** rivaroxaban may be considered a low solubility compound.
BE 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** **Background:** fasting study for the lower strengths, fed study for the higher strengths.
	Strength: 10 mg and 20 mg. **Background:** highest strength for a drug with linear pharmacokinetics and low solubility. Due to the

	different food effect at different strengths, studies with two strengths are required.
	Number of studies: two single dose studies. **Background:** since there is a different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths, two studies are required. One study under fasting conditions with the 10 mg strength and one study under fed conditions with the 20 mg strength are recommended.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	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 (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).