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Committee for Medicinal Products for Human Use (CHMP)

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

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Adoption by CHMP for release for consultation	24 September 2015
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* This revision relates to the deletion of the reference to low solubility in accordance with the ICH M13A guideline
** This guideline was previously published as part of a "compilation of individual product-specific guidance on demonstration of bioequivalence Rev.3 EMA/CHMP/736403/2014"

Keywords	***Bioequivalence, generics, rivaroxaban***

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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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 (MWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Rivaroxaban may be considered a low solubility compound.
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** **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, fasting study should be conducted for the lower strengths, and fed study for the higher strengths.

	Strength: 10 mg and 20 mg. **Background:** Highest strength for a drug with linear pharmacokinetics. Due to the different food effect at different strengths, studies with two strengths are required.
	Number of studies: Two single dose studies. **Background:** One single dose study under fasting conditions with the 10 mg strength and one single dose study under fed conditions with the 20 mg strength.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **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 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).