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

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| Draft agreed by Pharmacokinetics Working Party (PKWP) | July 2015 |
| Adoption by CHMP for release for consultation | 24 September 2015 |
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| End of consultation (deadline for comments) | 1 January 2016 |
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| Adoption by CHMP | 1 April 2016 |
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*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”

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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)*

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| **BCS Classification**** | **BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two**<br>**Background:** rivaroxaban may be considered a low solubility compound. |
| **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>**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. |

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| | **Strength:** 10 mg and 20 mg<br>**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<br>**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 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).