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Committee for Medicinal Products for Human Use (CHMP)

Acenocoumarol, tablet, 1 mg and 4 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	21 September 2020
Adopted by CHMP for release for consultation	15 October 2020
Start of public consultation	9 November 2020
End of consultation (deadline for comments)	28 February 2021
Agreed by Pharmacokinetics Working Party	11 March 2021
Adopted by CHMP	22 April 2021
Date for coming into effect	1 November 2021
Draft revision agreed by Methodology Working Party (MWP)	29 April 2025
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* This revision addresses the removal of the requirement for a chiral analysis in accordance with the ICH M13A guideline

Keywords	***Bioequivalence, generics, acenocoumarol***

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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 (PKWP)*

BCS Classification	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Acenocoumarol is 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**
	Strength: 4 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics.
	Number of studies: one

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** C_{max} and AUC_{0-t}
	90% confidence interval: 80.00 – 125.00% for C_{max} and 90.00 – 111.11% for AUC_{0-t} **Background:** Acenocoumarol is considered a narrow therapeutic index drug.

* 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.