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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 April 2022

Keywords	<i>Bioequivalence, generics, acenocoumarol</i>
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* The date of coming into effect has been extended due to a delay in publication.

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Acenocoumarol, tablet, 1 mg and 4 mg 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: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two Background: Acenocoumarol is considered a low solubility compound.
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: 4 mg Background: Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one

Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input checked="" type="checkbox"/> yes <input type="checkbox"/> no A chiral method is required to quantify both R (+) and S (-) enantiomers
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} Bioequivalence should be demonstrated for both enantiomers. 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.