EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2020
EMA/CHMP/512475/2020
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

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	
Adopted by CHMP	
Date for coming into effect	

Comments should be provided using this template. The completed comments form should be sent to PKWP@ema.europa.eu

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

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

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:** ☐ **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 and low solubility.
	Number of studies: one

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☒ **yes** ☐ **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.