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Committee for Medicinal Products for Human Use (CHMP)

Ezetimibe tablet 10 mg product-specific bioequivalence guidance

Draft

Draft Agreed by Pharmacokinetics Working Party (PKWP)	October 2018
Adopted by CHMP for release for consultation	13 December 2018
Start of public consultation	21 December 2018
End of consultation (deadline for comments)	30 June 2019

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

Keywords	***Bioequivalence, generics, ezetimibe***

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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.

B. Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Ezetimibe is almost insoluble in aqueous medium.
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: 10 mg **Background:** Only one strength available.

	Number of studies: One
Analyte	☐ **parent** ☐ **metabolite** ☒ **both** **Background:** Ezetimibe undergoes extensive pre-systemic metabolism; ezetimibe-glucuronide is the major active metabolite. Because of extensive hepatic recirculation, the exposure to ezetimibe is less representative to evaluate absorption.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, C_{max} **Background/justification:** On total (parent + glucuronide metabolite together)
	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.