EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Ezetimibe tablet 10 mg product-specific bioequivalence guidance

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
Draft Agreed by Pharmacokinetics Working Party (PKWP)	September 2019
Adopted by CHMP	19 September 2019
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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 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: 10 mg **Background:** This is the only available strength.

	Number of studies: One
Analyte	☐ **parent** ☐ **metabolite** ☒ **parent + metabolite** **Background:** Ezetimibe undergoes extensive pre-systemic metabolism into ezetimibe-glucuronide. Because of extensive hepatic recirculation, the exposure of ezetimibe is less representative to evaluate the rate of absorption than the metabolite. In this particular case, total (parent + glucuronide metabolite) should be used as analyte for bioequivalence evaluation.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, 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.