EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Ursodeoxycholic acid capsule 250 mg, film-coated tablet 150 mg, 300 mg, 450 mg, 500 mg, 600 mg and suspension 50 mg/ml (250 mg/5 ml) product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	7 October 2021
Adopted by CHMP for release for consultation	16 December 2021
Start of public consultation	17 December 2021
End of consultation (deadline for comments)	31 March 2022
Agreed by Pharmacokinetics Working Party	08 June 2022
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Keywords	***Bioequivalence, generics, ursodeoxycholic acid***

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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:** ursodeoxycholic acid (UDCA) is considered a low solubility compound
Bioequivalence study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: For capsules/tablets: the highest strength applied for. For suspension: 250mg/5ml should be studied. **Background:** For the capsules and tablets the highest strength for a drug with low solubility.

	Number of studies: one
Analyte	☒ **parent** ☐ **metabolite** ☐ **both** **Background:** Parent (free = unconjugated UDCA) is considered the most sensitive to detect differences in formulation.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
	Recommendations regarding method for baseline adjustment: 24 hours pre-dose baseline correction (same sampling scheme as on dosing day including meals, with individual matched sampling time-points).
Bioequivalence assessment	**Main pharmacokinetic variables:** baseline corrected AUC_{0-t} and C_{max} **Background/justification:** C_{max} should be pre-defined as highest peak within 0–12 h post-dose.
	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 intraindividual variability (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether in vivo studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: in vivo approach or in vitro approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85% within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).