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Committee for Medicinal Products for Human Use (CHMP)

Dronedarone film-coated tablets 400 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2017
Adopted by CHMP for release for consultation	22 June 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	31 October 2017
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Draft revision agreed by Methodology Working Party (MWP)	5 December 2024
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Start of public consultation	10 July 2025
End of consultation (deadline for comments)	31 October 2025

* This revision addresses the change in requirements from a fed study only to both fasted and fed studies in accordance with the ICH M13A guideline

Comments should be provided using this EUSurvey. For any technical issues, please contact the EUSurvey Support

Keywords	***Bioequivalence, generics, dronedarone***

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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:** Dronedarone hydrochloride is considered a low solubility compound with limited absorption.
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** **Background:** Dronedarone is considered a "high-risk product". Since the specific formulation (excipients) of the tablet is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test to reference formulations are required.

	A waiver for this fasted study may be applicable if it can be shown that the products are manufactured using the same technology and if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.
	Strength: 400 mg **Background:** 400 mg is the only available strength.
	Number of studies: Two single dose studies.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and 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.

** 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).