EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Dabrafenib hard capsule 50 and 75 mg product-specific bioequivalence guidance

Draft Agreed by Methodology Working Party (MWP)	02 February 2024
Adopted by CHMP for release for consultation	22 February 2024
Start of public consultation	11 March 2024
End of consultation (deadline for comments)	30 June 2024

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

Keywords	***Bioequivalence, generics, dabrafenib***

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Dabrafenib hard capsule 50 mg and 75 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 (MWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Dabrafenib is a low solubility compound with complete absorption.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**multiple dose** **cross-over** **patients:** stable patients with melanoma or non-small cell lung carcinoma (NSCLC). **Background:** A study in patients is recommended due to safety reasons.
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** **Background:** The SmPC recommends administration without food, at least 1 hour before or at least 2 hours after a meal.
	Strength: 75 mg. The therapeutic dose should be administered (2 x 75 mg twice daily).

	Background: Although the increase in exposure is less than dose-proportional after repeat twice daily dosing, probably due to induction of its own metabolism, the therapeutic dose is recommended in patients (two 75 mg capsules twice daily). Individuals on a lower dose can participate in the bioequivalence study as long as the same dose is administered to them throughout the study.
	Number of studies: one multiple dose study.
	Other design aspects: Minimum 14 days of dabrafenib administration prior to PK sampling. Co-medication of medicines that could affect the pharmacokinetics of dabrafenib should be avoided, if possible, and if not, their use should be well documented. A bioequivalence study for dabrafenib during combination therapy with trametinib is acceptable.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** $AUC_{0\text{-}tau}$ and $C_{max,ss}$
	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.