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SCIENCE MEDICINES HEALTH

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Trametinib film-coated tablet 0.5 and 2mg 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, trametinib***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Trametinib film-coated tablet 0.5 and 2 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:** Trametinib dimethyl sulfoxide is considered a low solubility compound.
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: 2 mg **Background:** 2 mg once daily is the recommended dose in patients. 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 critical aspects: Minimum 14 days of trametinib administration prior to PK sampling. Co-medication of medicines that could affect the pharmacokinetics of trametinib should be avoided, if possible, and if not, their use should be well documented. A bioequivalence study for trametinib during combination therapy with dabrafenib 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.