



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Vemurafenib film-coated tablets 240 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016
Agreed by Pharmacokinetics Working Party	December 2016
Adopted by CHMP	23 February 2017
Date of coming into effect	1 September 2017

Keywords	<i>Bioequivalence, generics, vemurafenib</i>
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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: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two Background: Vemurafenib is considered a low solubility compound.
Bioequivalence study design <i>in case a BCS biowaiver is not feasible or applied</i>	multiple-dose, cross-over
	patients
	<input type="checkbox"/> fasting <input checked="" type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed Background: There is a pronounced food effect for Zelboraf, administration with regard to food intake should be well controlled during the study.
	Strength: 240 mg Background: 240 mg is the only strength but the clinical dose of 960 mg BID should be used.
Number of studies: One multiple dose study (960 mg BID, administration with regard to food intake should be well controlled).	

	Other critical aspects: Achievement of steady-state conditions should be demonstrated. Co-medication of medicines that could affect the pharmacokinetics of Vemurafenib should be avoided, if possible, and should be documented well.
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: Multiple dose: $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$
	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.

** 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).