



1 21 July 2016
2 EMA/CHMP/476248/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Vemurafenib film-coated tablets 240 mg product-specific**
5 **bioequivalence guidance**

6 Draft

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

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Comments should be provided using this [template](#). The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

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Keywords	<i>Bioequivalence, generics, vemurafenib</i>
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13 **Vemurafenib film-coated tablets 240 mg product-specific bioequivalence guidance**

14 Disclaimer:

15 *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*
 16 *marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

17 **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>	single dose parallel
	Patients
	<input type="checkbox"/> fasting <input type="checkbox"/> fed <input checked="" type="checkbox"/> both <input type="checkbox"/> either fasting or fed Background: both fasting and fed are necessary due to specific formulation characteristics.
	Strength: 240 mg Background: 240 mg is the only strength but the clinical dose of 960 mg could be used.
	Number of studies: two single dose studies (fasting and fed) Other critical aspects: cancer treatment with vemurafenib could be started at day 4.

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: AUC ₀₋₇₂ and C _{max}
	90% confidence interval: 80.00– 125.00%

18 * As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to
19 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-
20 individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

21 ** 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
22 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
23 case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility
24 experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being
25 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
26 unacceptable differences in the excipient composition).