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Committee for Medicinal Products for Human Use (CHMP)

Lapatinib film-coated tablet 250 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2018
Adopted by CHMP for release for consultation	31 May 2018
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Keywords	<i>Bioequivalence, generics, lapatinib</i>
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* The date of coming into effect has been extended due to a delay in publication.



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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)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two</p> <p>Background: Lapatinib is a low solubility drug with limited absorption.</p>
<p>Bioequivalence study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>multiple dose</p> <p>cross-over</p>
	<p>Patients with breast cancer, whose tumours overexpress HER2 (ErbB2), for whom the drug is indicated.</p> <p>Background: A study in patients is recommended due to safety reasons.</p>
	<p><input type="checkbox"/> fasting <input type="checkbox"/> fed <input checked="" type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p> <p>Background: According to the SmPC of the reference product, lapatinib should be administered in a standardised manner at least 1 hour before food or at least 1 hour after food. There is a difference in absorption (2-3 fold difference in AUC) when lapatinib is administered 1 h before vs 1 h after a meal. Due to the strict requirement regarding standardisation of dosing in the individual patient, bioequivalence needs to</p>

	<p>be shown both under (semi-)fasting and semi-fed (1 hour after food) conditions.</p> <p>Strength: 250 mg. The therapeutic dose should be administered.</p> <p>Background: This is the only available strength.</p> <p>Number of studies: Two studies, one study in the fasting state (or semi-fasting 1 hour before a meal) and one study in a semi-fed state, i.e. 1 hour after a meal.</p> <p>Other design aspects: If the study is performed in patients who are treated with lapatinib in combination with capecitabine, pharmacokinetic sampling in each cycle is recommended during the latter part of the 7 day period when capecitabine is not administered (days 14-21), i.e. 3-5 lapatinib half-lives after the last dose of capecitabine in that cycle of treatment. Consecutive lapatinib trough levels should be measured to establish attainment of steady state.</p>
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	<p>Main pharmacokinetic variables: AUC_{0-tau} and C_{max, ss}</p>
	<p>90% confidence interval: 80.00 – 125.00%</p>

* 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 seem 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).