EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/CHMP/257298/2018
Committee for Medicinal Products for Human Use (CHMP)

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

Draft 2*

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2018
Adopted by CHMP for release for consultation	31 May 2018
Start of public consultation	27 June 2018
End of consultation (deadline for comments)	30 September 2018
Draft Agreed by Pharmacokinetics Working Party (PKWP)	June 2020
Adopted by CHMP for release for consultation	25 June 2020
Start of public consultation	6 July 2020
End of consultation (deadline for comments)	31 January 2021
Agreed by Pharmacokinetics Working Party (PKWP)	
Adopted by CHMP	
Date of coming into effect	

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

* This is the second public consultation after significant revision of the draft requirements in response to the comments from the first public consultation.

Keywords	***Bioequivalence, generics, lapatinib***

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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:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Lapatinib is a low solubility drug with limited absorption.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**multiple dose** **cross-over**
	Patients with breast cancer, whose tumours overexpress HER2 (ErbB2), for whom the drug is indicated. **Background:** A study in patients is recommended due to safety reasons.
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **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 1h before vs 1 h after a meal. Due to the strict requirement regarding standardisation of dosing in the individual patient, bioequivalence needs to

	be shown both under (semi-)fasting and semi-fed (1 hour after food) conditions.
	Strength: 250 mg. The therapeutic dose should be administered. **Background:** This is the only available strength.
	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.
	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.
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.

** 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).