12 November 2020
EMA/CHMP/567884/2020
Committee for Medicinal Products for Human use (CHMP)

Overview of comments received on 'Lapatinib film-coated tablet 250 mg product-specific bioequivalence guidance' (EMA/CHMP/257298/2018)

First public consultation

Interested parties (organisations or individuals) that commented on the draft document as released for consultation 27 June 2018 to 30 September 2018. A second consultation has subsequently been launched and these comments from the first consultation in 2018 are published for information now. The final overview of comments will take account of comments received in both consultations.

Stakeholder no.	Name of organisation or individual
1	Zentiva, k.s., Czech Republic
2	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland
3	Novartis

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We welcome the EMA initiative to issue product-specific guidance(s) to clarify the regulatory expectations regarding bioequivalence of certain products. Companies and other stakeholders also appreciate publication of received comments along with the PKWP feedback (outcome). However, for some products (namely ibuprofen and dimethylfumarate) neither the stakeholders' comments nor the feedback (outcome) from PKWP were published. The publication of comments as well as PKWP feedback (outcome) is considered essential to understand the rationale based on which the final requirements are laid. Also, in some cases, there were major changes introduced from draft to the final version of guidance (e.g., dabigatran etexilate or paliperidone palmitate) without the possibility of stakeholders to comment on the additional requirements. Therefore, the consultation process could be improved to enable at least 2 rounds of public comments in case of major changes (e.g., additional in-vivo studies are added). We believe this would be helpful for sponsors and would contribute to regulatory efficiency which translates to better access to affordable high-quality medicines for European patients.	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.
2	The Pharmaceutical Research Institute (PRI) is pleased to have the opportunity to comment on the draft Product-Specific BE Guidance released by the EMA. PRI has over 65 years of experience in pharmaceutical R&D (technology of API synthesis, drug dosage form, analytical services, registration). Pharmacokinetics Department (previously Pharmacology Department) of PRI conducts GLP compliant pharmacokinetic studies, including bioavailability and bioequivalence. The product specific bioequivalence guidances facilitate both preparation and evaluation of drug registration documentation. The presentation of data	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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	in the form of a table greatly facilitates reading. However, it would be appreciated if some more details, e.g. number of subjects and sampling schedule, would be recommended by the EMA for adoption by the applicant in specific cases. It is appreciated that the guideline deals with lapatinib, because its dosing regarding to meal intake does not follow standard approach. The EMA advise on selecting fasting and/or fed conditions for the bioequivalence study is appreciated.	
3	Novartis welcomes the opportunity to comment on the draft lapatinib product-specific bioequivalence guidance. In a nutshell, Novartis proposes the BE study to be conducted in naive patients eligible for lapatinib treatment or patients who are already on a regimen of oral lapatinib tablets within the approved combinations with the multiple dose, two-way, cross over study design. Further details are provided in the following comments section.	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 18 / Table Bioequivalence study design	1	**Comments:** We consider the proposed single-dose, cross-over study in healthy volunteers as well as the choice of primary pharmacokinetic metrics, study strength, analyte and achiral analytical method adequate for demonstration of bioequivalence for lapatinib. However, we have comments to the proposal to conduct studies both under fasting and fed conditions. Our position is summarized in the below paragraphs. Systemic exposure to lapatinib (Tyverb, EMEA/H/C/000795) is increased when administered with food. The bioavailability is approximately 2-3 times higher when lapatinib is taken 1 hour after food compared with 1 hour before the first meal of the day (SmPC of Tyverb). These were the conditions under which the drug was tested in pivotal efficacy and safety trials (Devriese, et al., 2014, Invest New Drugs 32: 481–488) and thus identical posology has been reflected in the prescribing information. Patients are instructed to standardise the drug administration in relation to food intake, for example always take the drug one hour before a meal (SmPC of Tyverb). As per EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), in those situations where SmPC allows the intake of reference medicinal product under fasting or fed conditions, the bioequivalence study should be conducted under fasting conditions as this	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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		represents the most sensitive condition to detect potential difference between formulations. Indeed, fasting conditions are most discriminative for lapatinib since factors like partitioning into fat, increased bile salts solubilisation and delayed gastric emptying under fed conditions will not interfere with the absorption process (Koch et al., 2000 J Clin Oncol 27: 1191-1196). Notably, to increase the sensitivity to detect differences between products, a fasting study is preferred over a fed one for another drug from the group of tyrosine kinase inhibitors, namely for imatinib (Glivec, EMEA/H/C/000406), even if the drug should be administered only with meal (Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg product-specific bioequivalence guidance, EMA/CHMP/315242/2014). The safety profile of lapatinib was assessed in pivotal clinical trials where the drug was administered either 1 hour before or 1 hour after food. Additional safety data were generated in smaller trials, where lapatinib was generally well-tolerated when administered with low or high-fat meal (Koch et al., 2000 J Clin Oncol 27: 1191-1196; Smith et al., 2003 Eur J Cancer 1:S169 (suppl; abstr 558); Devriese, et al., 2014, Invest New Drugs 32: 481–488). Should the conduct of fed study be enforced by PKWP due to safety concerns, the posology in this safety study needed to be aligned to the SmPC recommended conditions, i.e., lapatinib dose given at least one hour after a meal. Moreover, the acceptance criteria would have to be modified: it shall be demonstrated that the systemic exposure is not higher for the test product than for	

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		the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit. **Proposed change:** Table 'Requirements for bioequivalence demonstration (PKWP)': Section bioequivalence study design, in the recommendation regarding posology modify to: (1) ☒ fasting, ☐ fed, ☐either fasting or fed, and (2) in the section Number of studies, modify to: one single dose study.	
18 (*Bioequivalence study design* row in the table, fasting/fed conditions cell)	2	**Comments:** Recommendation on evaluating bioequivalence in both fasting and fed conditions seems to be unnecessary. 1. According to the EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) single fasting study should be performed for lapatinib because: a) The SmPC of the reference medicinal product recommends intake on an empty stomach ("at least one hour before food") or after meal ("at least one hour after food"). Thus reference product administration is irrespective of food intake and the bioequivalence study should be conducted under fasting conditions. b) The reference medicinal product is not product with specific formulation characteristics (e.g.	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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		microemulsions, solid dispersions). Thus it is not necessary to perform bioequivalence studies under both fasted and fed conditions. 2. Unnecessary exposure during second BE study rises serious ethical questions, because administration of lapatinib to healthy subjects results in high frequency of adverse events, see for example: a) Koch K. M. et al., J Clin Oncol. 2009; 27(8):1191-6 b) Burries III H. A. et al., Clin Cancer Res. 2009; 15(21): 6702–6708, c) Burries III H. A. et al., J Clin Oncol. 2005; 23(23):5305-13, d) Nakagawa K. et al., Jpn J Clin Oncol. 2009; 39(2):116-23). 3. Recommendation to conduct both fasting and fed studies seems to be not justified scientifically and it may negatively influence Patients' access to different products containing lapatinib. Due to rather high intra-subject variability of lapatinib (over 28%) and its BCS class II properties the number of subjects in bioequivalence study is predicted to exceed 70 for each study. Thus, cost of bioequivalence studies may limit development of generic drugs and decrease competition.	

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		Proposed change: ☒ fasting ☐ fed ☐ both ☐ either fasting or fed ~~The fed study should be a conventional fed study (high-fat high-calorie meal given 30 minutes prior to administration of drug product and finished within 30 minutes).~~ **Background:** ~~Both fasting and fed are necessary since lapatinib should be administered in a standardised manner with regards to food as systemic exposure to lapatinib is significantly increased when administered with food.~~ Lapatinib is administered in fasting (at least one hour before food) or fed conditions (at least one hour after food). Fasting conditions are more sensitive to detect potential difference between formulations and are related to less adverse events.	
Page 2; line 18 Bioequivalence study design: Single dose	3	**Comments:** Lapatinib is not recommended to be administered in healthy volunteers due to its hepatotoxicity (see comment no.3), thus the BE study needs to be conducted in patients for whom lapatinib is indicated (naive or already on lapatinib treatment). Therefore, One multi-dose study is proposed considering the adverse effects of lapatinib, and to measure the concentration of lapatinib after attaining steady-state. **Proposed change:** Add 'Multiple Dose once daily for 14 days' to replace 'single dose'	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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		Add 'Dose of lapatinib depends on the indication that is being treated. For combination with capecitabine, lapatinib dose will be 1250 mg (5 tablets); for combination with trastuzumab, lapatinib dose will be 1000 mg (4 tablets); and for combination with aromatase inhibitor, lapatinib dose will be 1500 mg (6 tablets) (see section 4.2 of Tyverb SmPC). Consecutive lapatinib trough levels are recommended to establish attainment of steady state.'	
Page 2; line 18 Bioequivalence study design: Cross-over	3	**Comments:** Novartis proposes to add 'Two-way' to the study design for clarity. **Proposed change:** Add 'Two-way' in addition to 'cross-over' study design Add 'Each patient would receive their dose of lapatinib using either the test or reference product in a crossover design.'	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.
Page 2; line 18 Bioequivalence study design: Healthy volunteers	3	**Comments:** Novartis proposes that subjects should be naive patients eligible for lapatinib treatment or patients who are already on a regimen of oral lapatinib tablets in combination with capecitabine, trastuzumab or aromatase inhibitors as indicated for the treatment of metastatic breast cancer whose tumours overexpress HER2 (ErBb2) (Tyverb SmPC section 4.1.) Due to the potential hepatotoxicity, lapatinib is not recommended to be administered in healthy volunteers. The hepatotoxicity-related warning & adverse reactions are	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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		included in the Tyverb EU SmPC. The recommendation also corresponds to the EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr, Jan-2010) section 4.1.3 that '*If the investigated active substance is known to have adverse effects, and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision*.' **Proposed change:** Please replace "Healthy Volunteers" by "Patients" in the Bioequivalence Study Design section.	
Page 2; line 18 Bioequivalence study design: Both (fasting/fed)	3	**Comments:** Following the proposed study design in patients with multiple dose daily for 14 days and consistent with Tyverb SmPC labelling, Novartis suggests that lapatinib should be administered either at least one hour before or at least one hour after food. **Proposed change:** ☒ Either fasting or fed Add ' lapatinib should be administered at least either one hour before or at least one hour after food' **Background:** ~~Both fasting and fed are necessary since~~ Lapatinib should be administered in a standardised manner with regards to food as systemic exposure to lapatinib is	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.

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		significantly increased when administered with food.	
Page 3; line 18 Bioequivalence study design: Number of studies Two single dose studies	3	**Comments:** Following the proposed study design, the fasting and fed condition are not applicable as well as two single dose studies. Fourteen days of dosing are proposed to ensure that patients have reached steady state of lapatinib. The PK matrix for BE assessment is AUC_{tau} (where tau = 24 hr) and C_{max} at steady state. Therefore, 24 hr sampling is adequate. **Proposed change:** Add 'One multiple dose study' to replace 'two single dose studies'; Add 'Collect 24-hour blood samples for steady state PK assessment from the last dose of 14 days of dosing' Remove 'Background: both a fasting and a fed study are needed.'	Draft guideline amended in line with all comments received and second public consultation launched 06 July 2020. This overview will be updated with the comments received in this second consultation.