25 July 2019
EMA/CHMP/681387/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Apixaban film-coated tablet 2.5 and 5 mg product-specific bioequivalence guidance' (EMA/CHMP/291499/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	STADA Arzneimittel AG
2	PharOS Ltd
3	Zentiva, k.s., Czech Republic

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table "Bioequivalence study design", section "Number of studies"	1	Comments: Whereas the proposed requirement of an additional study with crushed tablets apparently follows section 3.6 of the *"Clinical pharmacology and pharmacokinetics: questions and answers"* published by EMA, the scientific rationale for requesting such an additional study is not clear. Publicly available evidence does not seem to support such a requirement for the following reasons: 1. For the innovator product there is evidence published by the innovator company that crushing of those tablets has no impact on Cmax or AUC when the crushed tablets are administered with water (*Song Y et al. Evaluation of Crushed Tablet for Oral Administration and the Effect of Food on Apixaban Pharmacokinetics in Healthy Adults. Clin Ther. 2016 Jul;38(7):1674-168*). There is a slight decrease in Cmax/AUC when the crushed tablets are administered with apple sauce. However, this decrease in a similar extent was also seen in the usual food effect study in which the intact innovator product was administered after a high-fat high calorie-breakfast. Accordingly, there is a slight food effect for Apixaban which is, however, clinically irrelevant and therefore the innovator product can be administered also with apple sauce	Accepted. The statement *"An additional study may be required with crushed tablets, unless scientifically justified" has been deleted in line with the revised PKWP Q & A 3.6* https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers. The reference to 'with intact tablets' has also been deleted accordingly.

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		after crushing. Importantly, crushing of the tablets itself had no impact on AUC/Cmax. It is not understood where a difference between a crushed generic tablet and the crushed innovator tablet should come from, provided that bioequivalence of those products has been shown in a regular bioequivalence study conducted with the whole tablets as per CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. 2. Crushed tablets differ from the intact tablets mainly by the missing disintegration step which is "replaced" by mechanical manipulation. As such, a bioequivalence study with whole tablets encompasses all required steps from administration of the formulation to absorption including the formulation-specific disintegration step whereas a bioequivalence study with the crushed tablet does not. Therefore, a bioequivalence study with crushed tablets investigates largely the appropriateness of the applied manipulation technique together with the quantitative transfer of the dose rather than a formulation-specific characteristic. 3. To avoid bias in a crushed tablet-bioequivalence	

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		study with the goal to identify any potential formulation difference the manipulation and administration procedures have to be extremely standardized. However, the value of any evidence generated with such high standardization measures have questionable relevance for the therapeutic situation as it is reasonable to assume that patients will most likely not use highly standardized procedures for crushing the tablets. 4. In published literature there seem to be very few, if any, examples of bioinequivalence of crushed formulations which otherwise have been shown to be bioequivalent when administered as intact formulations. Proposed change (if any): Delete *"An additional study may be required with crushed tablets, unless scientifically justified."* In case that this proposal is not deemed acceptable, a more detailed reasoning of the scientific rationale would be appreciated.	
Table "Bioequivalence study design", section	1	Comments: The innovator tablet can be administered in different matrices after crushing the tablet. The current wording of the guidance is *"An additional study may be required with crushed tablets, unless scientifically*	See response to previous question.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
"Number of studies"		*justified*.", however it is unclear which kind of study is required. More specifically, if the requirement of such additional study is maintained then it would be appreciated to obtain more specific guidance on which administration conditions would be required to be applied in such a study. Would a study investigating crushed tablets in any matrix allow for extrapolation to the remaining matrices given in the SmPC of the innovator product? Proposed change (if any):	
Table "Bioequivalence study design", section "Number of studies"	1	Comments: The current wording of the guidance is "*An additional study may be required with crushed tablets, unless scientifically justified.*", however it is unclear which requirements such justification should meet. It would be highly appreciated if details would be added to this guidance on the evidence (e.g. kind of investigations, acceptance criteria etc.) which will be required to accept such justification. In this context, it is our current understanding that classification of Apixaban as BCS 3 does not appear to be one of those requirements as for Gefitinib no additional study is requested for the dispersed formulation in the respective draft product-specific guidance although Gefitinib is a low solubility drug.	See response to first question.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
19	2	Comment: As per Apixaban SmPC, for patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. As per the draft guideline, an additional study may be required with crushed tablets, unless scientifically justified. Given that more than one media for the administration of the crushed formulation are being suggested in the relevant SmPC, namely water, 5% dextrose in water (D5W), apple juice or apple puree, the most sensitive among the above in order to conclude with bioequivalence, allowing also waiving of the rest conditions need to be specified. Proposed change (if any): The most sensitive media to conduct the crushing bioequivalence study, allowing thus waiving of the rest conditions should be also specified.	See response to first question.
19-20, section BCS classification	3	Comment: Apixaban exhibits solubility which places it on the border of the BCS classification between highly and poorly soluble drugs. For this reason, we agree that if experimental data support BCS III classification, the	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		option of using a BCS biowaiver is adequate.	
19-20, section Number of studies	3	Comment: We consider the proposed single-dose, cross-over, fasting 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 Apixaban. However, it should be confirmed that the crushed tablet study can be waived in the situation when Apixaban is classified as BCS IV and in vitro data show no difference between the crushed Apixaban test and reference product. In vitro studies only to demonstrate similarity with the reference product when administered as dispersion in water (or through nasogastric tube) are considered sufficient in case of other poorly soluble drugs (e.g., Gefitinib film-coated tablet 250 mg, EMA product-specific guideline EMA/CHMP/257026/2018). This issue should be addressed in this product-specific guideline as it can be a source of disagreement among various assessors at different regulatory authorities. We believe that regardless of the BCS classification of Apixaban, in vitro data on crushed tablets is sufficient to prove similarity of the test and reference product and thus that any additional clinical trial assessing bioavailability after administration of formulations as crushed tablets is redundant.	See response to first question.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Our proposal is to modify the section Number of studies as following: „One single dose study with intact tablets. ~~An additional study may be required with crushed tablets, unless scientifically justified.~~ Additional in vitro studies testing crushed tablets should demonstrate similarity of the test product with the reference product.”	