22 April 2021
EMA/CHMP/133838/2021
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Palbociclib hard capsule 75 mg, 100 mg and 125 mg and film-coated tablet 75 mg, 100 mg and 125 mg product-specific bioequivalence guidance' (EMA/CHMP/802679/2018 Rev.1* Corr.1**)

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

Stakeholder no.	Name of organisation or individual
1	Medicines for Europe
2	Krka, d.d., Novo mesto

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
n/a	n/a	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
20	1	**Comments:** The new revision of the Palbociclib product-specific guidance introduces new requirements for the film-coated tablet formulation, specifically requiring a fasted bioequivalence study and a fasting study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI). It is questionable if the additional fasting study under conditions of pre-treatment with a PPI brings additional value to the assessment of safety and efficacy of generic film-coated tablets containing Palbociclib. From a regulatory point of view, there is no specific recommendation in the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr) with respect to requesting such coadministration studies in general. In this particular case, the reference product (Ibrance, film-coated tablets, marketing authorization holder: Pfizer Europe MA EEIG, Belgium) does not exhibit an effect of PPI coadministration on its in vivo pharmacokinetics putting the need for a fasting study under conditions of pre-treatment with a PPI in question. From a scientific point of view, it is clear from clinical data generated by the originator that there are	Not accepted. The capsule formulation of palbociclib is recommended to be administered with food in order to reduce variability in drug absorption ("low-liers" occur in the fasted state) and to mitigate drug-drug interaction with gastric acid-reducing agents. For approval of generic products to the capsule formulation, a study in the fed state is therefore recommended. The new tablet formulation contains a pH-regulating excipient in order to prevent the occurrence of low-liers under fasted conditions and eliminating the drug-drug interactions with gastric acid-reducing agents observed when the commercial capsule is administered following an overnight fast. Contrary to the capsule formulation, the tablet formulation may therefore be administered under fasting and fed conditions and allows PPI co-administration (also when taken in the fasted state). This can be considered a case of "special formulation characteristics" (the formulation has been modified in order to overcome issues with low-liers and interactions with gastric acid-reducing agents in order to allow administration with or without food), where the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) generally recommends fasting and fed studies. However, it is agreed with the stakeholder that a fed study would likely not be very informative in this case, as the food effect as such was not very large for the capsule formulation either, but food rather decreased the variability

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		differences between the pH-dependent Ibrance hard capsule formulation vs. the pH-independent Ibrance film-coated tablet formulation, especially when it comes to their behaviour when co-administered with PPIs, and also to a certain degree in the described food effects. Although the food effect is not identical between these two formulations, it seems clear that a meal (moderate-fat or high-fat) negates differences among various Palbociclib formulations, even when comparing a pH-dependent and pH-independent formulation. It is therefore very reasonable that no bioequivalence studies in fed state are required for Palbociclib film-coated tablet generics, as these would not help to describe differences among formulations and thus would be redundant and unethical to conduct. Therefore, the main area for discussion is the demonstration of similar behaviour in various pH conditions. In general, we question if an additional in vivo study is needed in the case when in vitro experiments may be sufficient to adequately describe the behaviour of formulations across the relevant range of pH. It is clear that the particularities of the Ibrance film-coated tablet formulation (e.g., the presence of succinic acid) change the way Palbociclib is released and/or solubilised, resulting in improved solubility thus leading to improved in vivo performance when co-administered with PPIs. Altered solubility characteristics across the typically tested pH range should thus be unique for pH-dependent formulations	seen in the fasted state. Instead, we recommend a fasted PPI study in addition to the regular fasted study. This is similar to the case of dabigatran etexilate, where the formulation is developed specially to allow co-administration of PPIs. Also, for dabigatran etexilate, the recommendation in the PSBGL is to perform a regular fasted study as well as a fasted study with PPI. Thus, this approach, although not the standard approach, has been used previously for dabigatran etexilate. As for dabitagtran etexilate (see PKWP Q&A 4.12), it is not agreed that dissolution tests at various pHs could replace the comparative bioavailability study with proton pump inhibitors as there is insufficient information on the relationship between in vitro dissolution of palbociclib and in vivo bioavailability of palbociclib in presence of proton pump inhibitors to establish an in vitro in vivo correlation (IVIVC) or a simple rank order correlation. The case of prasugrel referred to by the stakeholder is different, as the possible difference in effect of PPIs is mainly due to substance characteristics for prasugrel (different salt forms or base instead of salt), while for dabigatran and palbociclib this is due to formulation effects.

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		meaning that in vitro testing can actually be more sensitive to detect differences between formulations. We argue that a generic formulation could be first compared to Ibrance film-coated tablets primarily in vitro (e.g., dissolution experiments across the pH range of 1 – 6.8) and only if these experiments demonstrate that the two formulations behave differently, then a fasting study under conditions of pre-treatment with a PPI should be conducted. A similar approach has previously been adopted by PKWP in case of other poorly soluble drugs that display pH-dependent absorption (e.g., prasugrel, refer to Prasugrel hydrochloride film-coated tablets 5 mg and 10 mg product-specific bioequivalence guidance, EMA/CHMP/158772/2016/Rev.1). **Proposed changes:** In the table 'Requirements for bioequivalence demonstration (PKWP)', modify appropriate sections for tablet formulation as following: **Bioequivalence study design:** Tablets: In addition to the regular study under fasting conditions a fasting study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI), such as pantoprazole (40 mg b.i.d. for 4 days), is recommended unless scientifically justified considering in vitro data (e.g., dissolution profiles) and formulation.	

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		Number of studies: Capsules: One single-dose study (fed state) Tablets: One single-dose study (fasting state) unless an additional study under conditions of elevated gastric pH is needed based on evaluation of in vitro data.	
21 - Bioequivalence study design: Tablets	2	**Comments:** It is well recognised that for a drug exhibiting pH-dependent solubility; elevation of gastric pH by an acid-reducing agent may affect its absorption, leading to altered systemic exposure. The same goes for formulations designed specifically for overcoming problems of pH-dependent drug solubility within gastrointestinal tract (for example by incorporation of a pH modifier). There is however no need for performance of in vivo studies as a rule for each and every case of potential difference between generic and reference product arising from pH dependence. In the past few years several attempts have been made to set conceptual framework (1, 2, 3) for assessing the need for in vivo Drug-drug interaction studies using in vitro determined factors. In vitro dissolution similarity together with functionally equivalent formulation composition can be considered suitable approach to ensure in vivo bioequivalence and, hence, therapeutic equivalence. This approach is already well acceptable by EMA for Biowaivers for BCS I and III class drug and also for additional strength	Not accepted. See previous comment.

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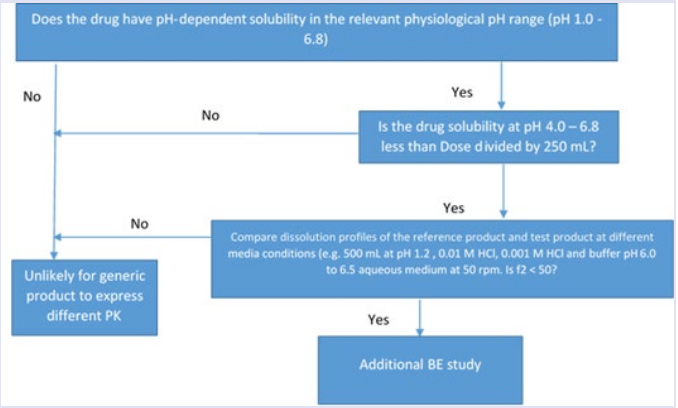
		within product series. For both approaches, criteria are well defined. It is our opinion that selective and well-defined in vitro approach can be used to predict potential need to study differences between generic and innovator product in vivo through study performed with gastric pH modifier. The following decision tree is suggested:  The reference pH of 6.0-6.5 is selected because it represents the highest gastric pH that a PPI may achieve at its labelling-recommended doses (1). The proposed dissolution media therefore simulate borderline conditions in the stomach after single and multiple administration of PPI. Namely, selected dissolution media reflect not only the change in pH but also suppressed gastric acid secretion and by that reduced buffer capacity of gastric fluid. Therefore, not only pH dependent dissolution is tested but also effect	

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		of formulation on medium pH and by that solubility of drug. In cases like this, in vitro studies are a good surrogate for in vivo comparisons. The pH value of 6.0-6.5 (1) is considered applicable also for palbociclib as a suitable medium biorelevant for conditions of elevated gastric pH reflecting border conditions in vivo under fasting condition and co-administration of PPI. Proposed set of in vitro dissolution studies might be supported by in vitro comparisons of originator's capsules and/or tablet formulations for which effect of PPI on Cmax and AUC has been evaluated by the originator. Specifically for palbociclib, a study performed under standard fasting conditions without coadministration of PPI can detect problems of limited solubility under elevated pH. There is always a good chance to include some subjects with higher basal gastric pH values. This occurance was also reported by originator who detected so called »low liers«, i.e. subjects exhibiting low palbociclib plasma profiles comparable to profiles obtained under effect of PPI pretreatment, in his studies performed on pH susceptible capsule formulation (4). Therefore, on can reasonably conclude that beside adequate bioequivalence under fasting condition, comparative dissolution profiles in proposed dissolution media will assure adequate and	

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		comparable in vivo pharmacokinetic profile of generic formulation to reference product also after co-administration of PPI under fasting condition. **Proposed changes:** **Bioequivalence study design** Tablets: In addition to the regular study under fasting conditions - an adequate set of in vitro dissolution studies should be conducted and similarity of dissolution profiles between formulations should be established or - a fasting study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI), such as pantoprazole (40 mg b.i.d. for 4 days), should be conducted. **Number of studies:** Tablets: One single-dose fasting study. Eventual additional study under conditions of pre-treatment with a PPI is needed if adequate set of in vitro dissolution studies does not demonstrate similarity between formulations.	

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		References: 1) L Zhang (et all): pH-Dependent Drug-Drug Interactions forWeak Base Drugs: Potential Implications for New Drug Development; Clinical Pharmacology & Therapeutics, Vol. 96 (2),2014, 266-277 2) Masahiko Sato (et all): Predictive factors for the effect of acid-reducing agents on drug exposure; International Journal of Clinical Pharmacology and Therapeutics, Vol 55 (10), 2017, 198-808 3) Guidance for Industry: Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) November 2020 4) Garcia at all: Effect of food on the bioavailability of palbociclib; Cancer Chemother Pharmacol; 79, 2017; 527-533	