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Committee for Medicinal Products for Human Use (CHMP)

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

Draft Agreed by Pharmacokinetics Working Party (PKWP)	October 2018
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*This revision concerns the addition of requirements for a tablet.

Keywords	***Bioequivalence, generics, palbociclib***

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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:** Palbociclib is considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	Capsules: ☐ **fasting** ☒ **fed** ☐ **both** ☐ **either fasting or fed** Tablets:

	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** 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), should be conducted. **Background:** Solubility of palbociclib is pH dependent. PPIs may affect the bioavailability of palbociclib under fasting conditions differently depending on the formulation.
	Strength: 125 mg **Background:** Highest strength for drugs with linear pharmacokinetics and low solubility.
	Number of studies: Capsules: One single-dose study (fed state) Tablets: Two single-dose studies (fasting and under conditions of pre-treatment with a PPI).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** $AUC_{0\text{-}72h}$, C_{max}
	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 seems 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).