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Committee for Medicinal Products for Human Use (CHMP)

Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance

Draft

Draft agreed by Pharmacokinetics Working Party (PKWP)	June 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of public consultation	3 August 2017
End of consultation (deadline for comments)	31 October 2017

†This revision concerns the addition of 'T_{max}' as an additional main pharmacokinetic variable in the bioequivalence assessment section of the guideline.

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

Keywords	***Bioequivalence, generics, tadalafil***

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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:** Tadalafil 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
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **Background:** The reference product can be taken with or without food according to the SmPC. Since, the specific formulation (e.g. particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, following the requirements for "specific formulation characteristics" described in the Bioequivalence Guideline, both fasted and fed state comparisons of test to reference formulations are

	required.
	Strength: 20 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: Two single dose studies (20 mg fasted and 20 mg fed)
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, C_{max} and T_{max}
	90% confidence interval: 80.00 – 125.00% for AUC_{0-72h} and $C_{max.}$ Comparable median and range for $T_{max.}$

* 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).