25 January 2018
EMA/CHMP/644909/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance' (EMA/CHMP/315234/2014/Rev.1)†

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

Stakeholder no.	Name of organisation or individual
1	Alembic Pharmaceuticals Limited
2	European Association of Hospital Pharmacists (EAHP)
3	Zentiva, k.s., Czech Republic

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	EAHP supports the additional requirements for bioequivalence demonstration.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
20 - Bioequivalence assessment	1	Comment: The bioequivalence assessment section of the guideline has been revised to include the 'T_{max}' as an additional main pharmacokinetic variable. The term 'comparable median and range for T_{max}' should be specified with acceptance criteria i.e. time difference should not be more than xx minutes or any specific statistical tool through which comparability can be confirmed.	Not accepted It is not possible to give an absolute value in minutes for the acceptance range of T_{max} because this depends on the result obtained for the T_{max} of the reference in the study under assessment. The T_{max} values of the reference product differ between the fed state study and the fasted state study. Even the studies in fasted state submitted by different applicants have exhibited different T_{max} values, e.g. from 2.0 to 3.2 hours. No specific statistical tool could be defined in the guideline because the comparison is not based on any statistical test according to the Guideline on the investigation of bioequivalence, but simply on the numerical comparison of medians and ranges.
Line 20 Table / Bioequivalence assessment	3	**Comment:** Tadalafil has a unique pharmacokinetic profile with a mean terminal half-life of 17.5 hours (Forgue et al., 2005; SmPC Cialis, EMEA/H/C/000436). This pharmacokinetic profile led to a proposal that tadalafil may be effective for a longer period of time (Young et al., 2005) as compared to other phosphodiesterase 5 (PDE5) inhibitors. A number of phase 3 studies have demonstrated efficacy of tadalafil up to 36 hours post-dosing. In brief, in a double-blind, placebo-controlled cross-over study, a significantly higher percentage of patients (59%) on tadalafil 10 mg were able to achieve an erection 24 hours after dosing,	Not accepted. T_{max} is considered relevant for the onset of action, the longer period of effectiveness due to its long half-life is not relevant for this discussion.

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		compared to patients taking placebo (7%) (P=0.001), as assessed by penile plethysmography evaluations (Padma-Nathan et al., 2003). In a multicentre, randomized double-blind study in 348 men with erectile dysfunction (ED), tadalafil at a dose of 20 mg was shown to significantly improve patients' ability to complete successful sexual intercourse at 24 as well as at 36 hours post-dose, compared to placebo treated patients (Porst et al, 2003). In another phase 3 study conducted across 38 clinical sites in the United States, the efficacy of tadalafil was assessed at 2 pre-specified assigned times of 24 and 36 hours post-dosing. Significant difference versus placebo has been shown at both doses and at both 24 and 36-hour time points (Young et al., 2005). Retrospective analysis of eleven phase 3 trials also confirmed efficacy between 24 and 36 hours after tadalafil 20 mg (Carson et al., 2004). These studies clearly demonstrated that efficacy is maintained far beyond TMAX, when plasma concentrations drop to more than threefold less than the CMAX (Shabsigh et al., 2006). After oral administration of tadalafil on fasting conditions, the maximum observed plasma concentration (CMAX) is achieved at a median time of 2 hours after dosing (range 0.5 – 6 hours) (Gupta et al., 2005). Previous reports suggested that the time to erectogenic effect may be significantly less than it would be expected based on the specific	It is known that the pharmacodynamic effect and the plasma concentration time profile do not follow the same pace in most drugs. This only occurs when e.g. the effect depends on the plasma concentration without any delay caused by signal transduction. Even in that case the time to the effect will not agree with T_{max} since it is expected that the minimum effective concentration will be lower than T_{max}. Consequently,

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		pharmacokinetic parameters such as TMAX. Compared to placebo, a significant erectogenic response to tadalafil 20 mg was found from 30 minutes down to 16 minutes after dosing (P<0.012) (Rosen et al., 2004). Thus, the erectogenic effect is not predicated on the need to reach CMAX. In summary, the above reviewed studies have demonstrated that a significant effect of tadalafil is achieved prior to reaching the maximum plasma concentration (that is, prior to TMAX) and is lasting far beyond this point. As per EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), statistical analysis of Tmax is not required unless rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events. This is obviously not applicable for tadalafil and thus there is no need to require comparable median and range for TMAX in bioequivalence studies. **Proposed change:** In the table 'Requirements for bioequivalence demonstration (PKWP)': Section Bioequivalence assessment, delete the corresponding text related to TMAX: ~~Comparable median and range for Tmax.~~ **References** Carson, C.C., et al. (2004). BJU Int 93(9): 1276 –	what is described here for tadalafil is very frequent in many other drugs. It is agreed that the effect can be found much earlier than T_{max} (e.g. 15-30 minutes after dosing vs. 1-2 hours) and that C_{max} does not need to be reached to observe the pharmacological erectogenic effect. The fact that the pharmacological effect is observed before T_{max} and is lasting after T_{max} is not a reason to consider that T_{max} is clinically insignificant. T_{max} is considered clinically relevant because T_{max} is used as a surrogate for rate of absorption and a product with a longer T_{max} will reach effective concentrations (onset of action) later. For example, a product with a T_{max} of e.g. 4 hours is expected to reach effective plasma concentrations (onset of action) later than a product with T_{max} of e.g. 2 hours. As the onset of action is considered clinically relevant for the erectogenic effect, T_{max} needs to be considered as a primary pharmacokinetic endpoint.

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		1281 Forgue, S.T., et al. (2005). Br J Clin Pharmacol 61(3): 280 – 288 Gupta, M., et al. (2005). J Clin Pharmacol 45(9): 987 – 1003 Padma-Nathan, H., et al. (2003). Am J Cardiol 92(9A): 19M-25M Porst, H., et al. (2003). Urology 62(1): 121 – 126 Rosen, R.C., et al. (2004). J Sex Med 1(2): 193 – 200 Shabsigh, R., et al. (2006). Urology 68(4): 689 – 696 SmPC Cialis, EMA product number EMEA/H/C/000436, last updated on 24/05/2017 Young, J.M., et al. (2005). J Androl 26(3): 310 – 318	