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Tadalafil T_{max} – case study

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T_{max} – A fairly tale

Let’s set-up the scene:

- According to the EMA BE Guideline…*A statistical evaluation of Tmax is* (usually) *not required*
- *T_{max} is considered a primary PK parameter only in the exceptional cases where onset of action is clinically relevant* (WHO Guidance, 2020)
- If you want to go through this topic, you can enter into a universe of experts: *https://bebac.at/articles/%E2%80%98Apparent%E2%80%99-Difference-in-tmax.phtml*

Good luck!

Tadalafil Bioequivalence Guideline: A long story

- 25 July 2013: Concept paper on the development of product-specific guidance on demonstration of bioequivalence
- 15 November 2013: Tadalafil Product-Specific Bioequivalence Guidance (**draft**): AUC_{0-72h}, and C_{max}
- 25 May 2016: Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 4 20 mg product-specific bioequivalence guidance: Main pharmacokinetic variables **(First version)**: AUC_{0-72h}, and C_{max}
- 20 July 2017: Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance (**Rev 1, draft**): AUC_{0-72h}, C_{max} and T_{max}

Tadalafil Bioequivalence Guideline: A long story

25 January 2018: Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance (**Comment to Rev 1, draft**): Strong opposition to the inclusion of T_{max}: T_{max} is considered relevant for the onset of action, despite that it was agreed that "…the effect can be found much earlier than T_{max} (e.g., 15-30 minutes after dosing vs. 1-2 hours)…" , but "…T_{max} is considered clinically relevant because T_{max} is used as a surrogate for rate of absorption"…

01 August 2018 (**legal effective date**): Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance (**Rev 1**): AUC_{0-72h}, C_{max} and T_{max}

04 April 2022**:** Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-spec bioequivalence guidance (**Rev 2, draft**): AUC_{0-72h}, C_{max} and T_{max} (This revision concerns defining what is meant by 'comparable' T_{max} as an additional main PK variable in the bioequivalence assessment section of the guideline).

Tadalafil Bioequivalence Guideline: A long story

- 26 April 2023: Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance (**Comment to Rev 2, draft, adopted the same day**): Strong opposition to the inclusion of T_{max}

Some examples:

- We would like first of all to understand the reasons for proposing a T_{max} in the first place…
- T_{max} is a poor predictor of any differences in the rate of absorption and an even worse one regarding the onset of action…
- The new proposal for acceptance criteria for median of T_{max} was introduced based on disagreement in registration procedure (IE/H/1132/001/DC) that involved ibuprofen formulations…this particular case (*wrongly*) represents a precedent for definition of general criteria…

Tadalafil Application: Where is the mistake?

- 21 June 2022: T_{max} median and range were not discussed in the final study report, which is not in line with the current guidance on tadalafil bioequivalence assessment (EMA/CHMP/315234/2014/ Rev.1)….

Although acknowledging that **the study was conducted before the product specific guideline came into effect**, at the present time and considering the current guideline, a faster absorption rate with the capsule formulation under fed conditions may compromise the acceptability of this new tadalafil formulation as a generic product of *Cialis 20 mg film-coated tablets…*

Tadalafil Application: Do not panic!

01 The observed values of C_{max} for both products are in line with those obtained in a published in 13 clinical pharmacology studies…

02 Tadalafil was absorbed rapidly with a mean C_{max} (378 ng/ml at 20 mg) occurring at a median t_{max} of 2 h (identical to the arithmetic mean of t_{max} of the test product in both fast and fed conditions)…

03 The proposed formulation (test) yielded a shorter median t_{max}, however the range (1 - 4.5 h) is still within the range of the reference product (1-12 h). Therefore it can be safely assumed that based on the T_{max} it can be expected that the test and the reference product will have similar onset of action…

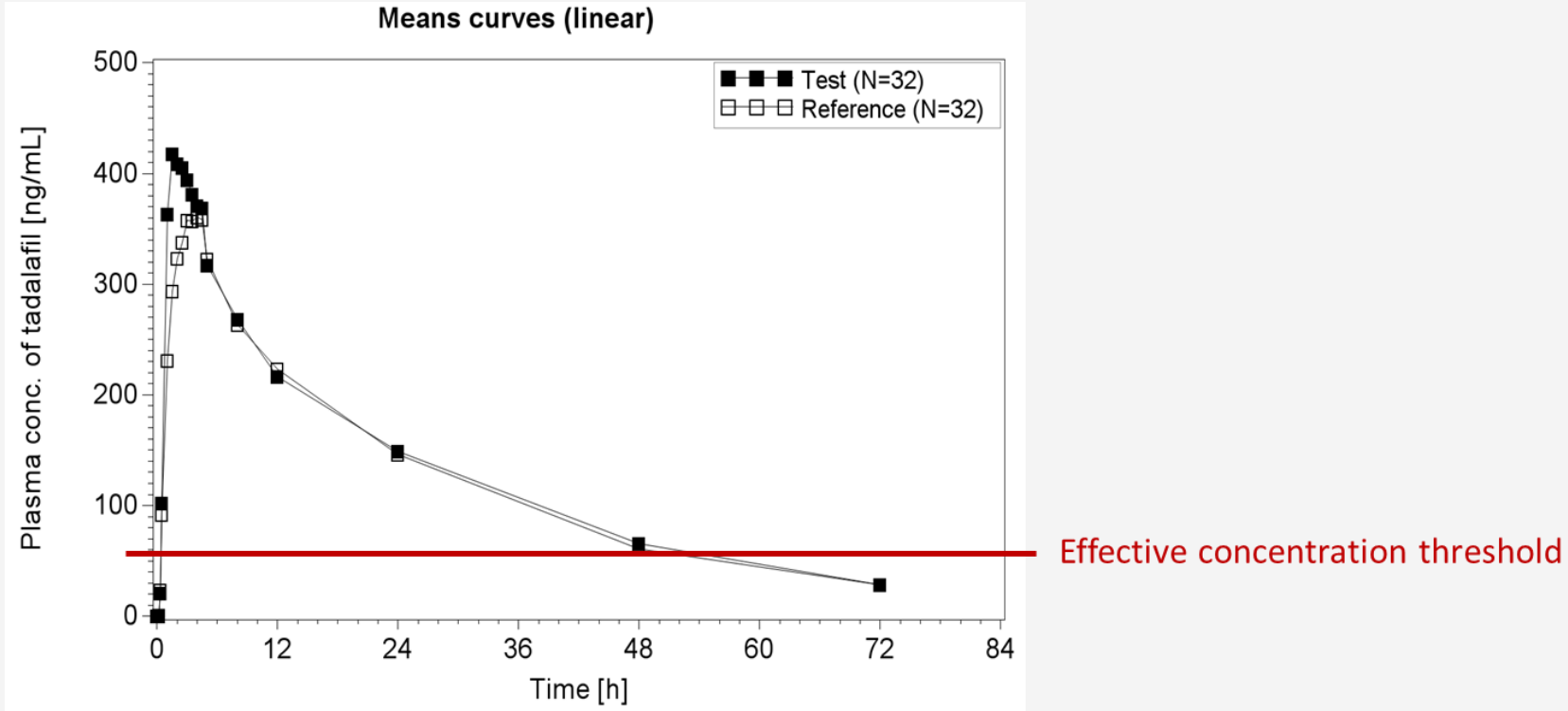
Tadalafil Application: Do not panic!

04 The clinical significance of slight differences in the rate of absorption are negligible in case of tadalafil. The reason for this is that there seems to be no correlation between the rate of absorption and pharmacodynamic effect…the onset of action of tadalafil is seen long before C_{max} is reached…(*and*)…the erectogenic effect of tadalafil remains long after maximum concentrations have been reached…

05 …it seems that the time range for the onset of action of tadalafil is anywhere between 30 min and 36 hours…

Tadalafil Application: Do not panic!

A graphical presentation of the efficacy threshold in relation to the mean concentration vs. time curves is presented (during the development of the originator, effective concentration threshold determined as a reasonable pharmacodynamic target was 55 ng/ml based on 90 % enzyme inhibition *in vitro)*:



Tadalafil Application
A friendly end: When reason prevails

RMS agrees with the Applicant that **the study results are acceptable**, supporting the bioequivalence conclusion of the proposed tadalafil formulation relative to the Reference product, *Cialis 20 mg film-coated tablets.*

Issue solved.

Tadalafil Application
A friendly end

My sincere thanks to Marina Fertek for her valuable help in the solution of this case!!

Thank you for your attention