Reviewer's report

Title: Cardiovascular Risks and Elevation of Serum DHT Vary by Route of Testosterone Administration; a Systematic Review and Meta-analysis

Version: 1
Date: 19 September 2014
Reviewer: Farid Saad

Reviewer's report:

This is a very interesting and novel report on the relationship between testosterone treatment and cardiovascular risk. For the first time, investigators look at different routes of testosterone administration and the impact that the conversion of testosterone to DHT may have on cardiovascular outcomes.

1. (Minor Essential Revisions)

On page 4, the authors state that "Testosterone can be administered ... orally as testosterone undecanoate (TU)." While testosterone undecanoate capsules are one of very few approved testosterone preparations for oral use, one of the four studies analysed in this manuscript is the so-called Copenhagen Study (reference 32). In this study, compounded micronized testosterone was administered which was never approved in any country. Moreover, this preparation was administered at very high doses to men with liver cirrhosis, resulting in peak testosterone levels of approximately 700 nmol/L, about 20 times the upper range of normal. In a meta-analysis of testosterone treatment, this study is obviously of an experimental nature and should not be treated equal to all other studies, at least not without pointing out that this is outside of any use of testosterone within the given labels. Since this is one out of only four studies on oral preparations, the interpretation of the apparently higher cardiovascular risk of oral preparations must be made with caution.

2. Minor Essential Revisions

On page 8 and prior to the Discussion, the authors state that "oral TRT appeared to produce a post-treatment serum T that was similar with other administration routes". The Copenhagen study resulting in supraphysiological levels was already discussed above. In Chapman's paper (ref. 65), there was a decline of T levels despite treatment with oral TU. In Emmelot-Vonk's study (ref. 66), testosterone was unchanged from baseline after 6 months of treatment. In Legros' paper (ref. 67), to my knowledge, T levels post treatment were not reported. All in all, T levels achieved under treatment with oral TU are very different from i.m. and transdermal preparations.

3. Discretionary Revisions

The authors may consider to also discuss in their introduction regarding different routes of administration that adherence to study medication may differ. Revent
reports by Schoenfeld et al. (J Sex Med 2013;10:1401–1409) and Donatucci et al. (J Sex Med 2014;11:2092–2099) suggest that adherence to transdermal preparations is far from optimal which may also play a role in the differentiation between various routes of administration.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am a full-time scientific employee of Bayer Pharma AG, manufacturers of testosterone products.