NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Estonia:

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	All strengths All pharmaceutical forms
Active Substance(s)	Testosterone-containing medicinal products (including esters and salts)
Marketing Authorisation Holder(s)	Various

The primary indication for androgens, such as testosterone or its esters, is replacement therapy in male hypogonadal disorders caused by either pituitary or testicular disorders or in hypogonadism following orchidectomy.

Testosterone may also be used to promote masculinisation in hypogonadal adolescent boys, and is of value in the prevention of osteoporosis in hypogonadal men. Transdermal testosterone may possibly be of benefit as an adjunct to oestrogen replacement in *women* who have undergone hysterectomy and oophorectomy. There has also been growing interest in the use of testosterone therapy in *healthy older men*, although there is limited evidence to prove a direct association between clinical changes and the natural decline of endogenous hormone concentrations with age.

Testosterone, as well as other androgens and anabolic steroids should be used cautiously in patients with cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possible fluid retention or oedema caused.

Recent concerns have arisen about an increased risk of cardiovascular events associated with testosterone therapy (TT). Namely increased risk of myocardial infarction in men who are receiving TT and who have pre-existing heart disease as suggested by a recent study by Finkel at al[1]. This study suggested a two-fold increase in the rate ratio of myocardial infarctions (MI) in the 90 days after starting TT in men who had heart disease compared to the year before. The increase in MI was even greater in men over the age of 65 than in men under the age of 65.

This study follows the findings of another study from the Veterans Health Care System[2], which also found a higher frequency of death and cardiovascular events in men who had documented coronary artery disease and who were on TT. In addition, a search in bibliographic databases has identified a meta-analysis "Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials", which showed that testosterone increased the risk of cardiovascular-related events.

Overall, these studies have heightened concern about the safety of testosterone therapy namely the increased risk for serious cardiovascular events. Therefore, there is a need to perform an European review to evaluate the impact of this increased risk for cardiovascular events in the benefit-risk of testosterone containing medicinal products in its approved indications to conclude whether the Marketing Authorisations for testosterone containing medicinal products should be maintained, varied, suspended or withdrawn and to ensure that appropriate risk minimisation measures are in place to optimize the benefit –risk balance if appropriate.

Based on the increased risk of cardiovascular events described above, Estonia therefore considers that it is in the interest of the Union to refer testosterone containing medicinal products to the PRAC/EMA and to request its opinion under Article 31 of Directive 2001/83/EC, on whether the Marketing Authorisations for testosterone containing medicinal products should be maintained, varied, suspended or withdrawn.

[redacted]

Date 27.03.2014

---

1 **Finkle et al.** "Increased risk of non-fatal **myocardial infarction** following testosterone therapy prescription in men." PLoS One. 2014

2 Vigen et al. "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels." JAMA. 2013 Nov 6;310(17):1829-36.