

Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations subject to conditions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Scientific conclusions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CMDh considered the below PRAC recommendation with regard to testosterone containing medicinal products:

1 - PRAC recommendation

Overall summary of the scientific evaluation by PRAC

Testosterone is an androgenic hormone secreted by the Leydig cells in the testis. It is an essential hormone for the development of male reproductive tissues as the testis and the prostate and in promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair (*Dollery et al., 1991*¹).

Hypogonadism in men is a congenital or acquired syndrome, in which the testis fails to produce physiological levels of testosterone and spermatozoa, as there is a disruption in the hypothalamic-pituitary-testicular axis (HPT).

Hypogonadism is classified into primary testicular failure due to a problem in the testicles and secondary testicular failure, due to a problem in the hypothalamus or the pituitary gland. The clinical symptoms depend on the age of onset androgen deficiency. If the hypogonadism develops before puberty e.g. as part of a genetic disease, the men will exhibit eunuchoid proportions, delayed of secondary sex characteristics and high pitched voice. The symptoms are less specific if the hypogonadism develops after puberty and are characterized by e.g. decreased sexual function, infertility, decreased energy, depressed mood, mild anaemia, reduced muscle bulk and strength, increase body fat and BMI (guideline of Endocrine Society).

The major goal of testosterone therapy (TT) is to achieve normal physiological levels of testosterone levels to relieve symptoms of hypogonadism like decreased sexual function, infertility, decreased energy, depressed mood, mild anaemia, reduced muscle bulk and strength, increased body fat and body mass index (BMI) and psychological impairment. There are no treatment alternatives to testosterone for male hypogonadism (*Buvat et al. 2013*²).

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.

Concerns were raised with regards to a potential increased risk of cardiovascular events, namely myocardial infarction, in men treated with testosterone and who have pre-existing heart disease (*Finkle et al, 2014*³; *Vigen et al, 2013*⁴ and *Xu et al, 2013*⁵). A referral under Article 31 of Directive

¹ Dollery C, Boobis AR, Burley D, Davies DM, Davies DS, Harrison PI, Orme ML, Park BK, Goldberg LI eds. Therapeutic drugs. Edinburgh: Churchill Livingstone, 1991; T20-1

² Buvat J, Maggi M, Guay A, Torres LO. Testosterone Deficiency in Men: Systematic Review and Standard Operating Procedures for Diagnosis and Treatment. *J Sex Med* 2013; 10: 245–284.

³ Finkle et al. "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men." *PLoS One*. 2014.

⁴ 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.

⁵ Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013; 11:108.

2001/83/EC was therefore initiated, to review the benefit-risk balance of testosterone containing medicinal products.

All testosterone-containing medicinal products approved in the European Union were included in this review performed by the PRAC. All were authorised nationally and are available in different pharmaceutical forms: solution for intramuscular injection, oral capsules, cutaneous gel, cutaneous solution and transdermal patch.

The PRAC reviewed all data available from clinical trials, observational studies, meta-analyses, post-marketing data and further published data on the cardiovascular risks associated with testosterone therapy.

The PRAC acknowledged that some studies show an increased risk of cardiovascular events in men treated with testosterone. The PRAC noted that the findings from several other observational studies, clinical trials and meta-analysis of randomised clinical trials do not provide evidence of an association between testosterone and cardiovascular events. As an example, recently published studies (*Baillargeon et al., 2014⁶; Corona et al., 2014⁷; Tan et al., 2014⁸; Hildreth et al., 2013⁹*), with the objective to examine the risk of cardiovascular events with TT, did not report an increase in this risk. Also, the RHYME study, an observational registry study performed in 6 European countries evaluating the association between TT (over two years) and prostate health outcome in men with hypogonadism also looked at health outcomes, as secondary endpoints. Results suggest that rates of prostate cancer and cardiovascular events were within the anticipated range, with no evidence of increased risk in treated versus untreated patients.

The studies and their limitations were considered together with the overall evidence available to date.

Overall the PRAC concluded that the findings in the literature do not consistently show an increased risk of cardiovascular events and do not corroborate the signal of an increased risk of cardiovascular events associated with testosterone therapy. Therefore, taking the totality of data into account it is judged that the signal for an increased cardiovascular risk associated with the use of testosterone remains weak and inconclusive. It is expected that the marketing authorisation holders continue to monitor cardiovascular events and it is expected that findings of ongoing studies will be reflected in periodic updated safety reports (PSURs) when available. The Committee recognised the limited available information on testosterone therapy for age-related hypogonadism and also the lack of reference. Further studies will be needed to provide relevant safety and efficacy data in this patient population.

It is known that in patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately. The PRAC also recognised that testosterone may have both direct and indirect effect on the cardiovascular systems: low testosterone increases the risk of the metabolic syndrome, which could potentially increase the risk of adverse cardiovascular events. On the other hand, testosterone stimulates red blood proliferation, which theoretically could increase the risk of thromboembolic events. Given the

⁶ Baillargeon J, Urban RJ, Kuo Y-F, Ottenbacher KJ, Raji MA, Du F, Lin Y-I, Goodwin JS. Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother* 2014; 48(9):1138-1144.

⁷ Corona G, Maseroli E, Rastrelli G, Isidori A, Mannucci E, Maggi M. Cardiovascular risk associated with testosterone boosting medications: a systematic review and metaanalysis. *Exp Opin Drug Safety* 2014 (Posted online on August 19, 2014. (doi: 10.1517/14740338.2014.950653)

⁸ Tan R, Cook KR, Reilly WG. Testosterone therapy is not associated with higher risk of myocardial infarction or stroke: The low T experience. Abstract Book of the 2014 Annual Meeting of the American Association of Clinical Endocrinologists (AACE), pg 238, abstract # 1353; available at: <https://www.aace.com/files/late-breaking-abstracts-2014.pdf>

⁹ Hildreth KL, Barry DW, Moreau KL, Vande Griend J, Meacham RB, Nakamura T, Wolfe P, Kohrt WM, Ruscini JM, Kittelson J, Cress ME, Ballard R, Schwartz RS. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab* 2013; 98(5): 1891-1900.

knowledge to date, the PRAC recommended that the possible mechanism on the association between cardiovascular/venous thromboembolic events and the level of testosterone be further investigated by the marketing authorisation holders and reported at the next PSUR.

Testosterone should be used with caution in men with hypertension and testosterone levels should be monitored both at baseline and at regular intervals during treatment to ensure the adequacy of the dose administered. In addition, there is limited experience on the safety and efficacy of the use of testosterone in patients over 65 years of age. The marketing authorisation holders are requested to investigate and report in the next PSUR on the usage of these products in this patient population and to consider if the pattern of adverse events is comparable to other age groups.

The next PSUR, will have the common DLP to all testosterone-containing medicinal products of 31 December 2015.

Based on all the above discussed, the PRAC considered justified to reflect in the product information of all testosterone containing medicinal products approved in the European Union that prescribing testosterone for hypogonadism should be based upon confirmation of both clinical features and biochemical testing. Information on the cardiovascular safety and well-documented blood system adverse reactions, which may contribute to the cardiovascular risk should be included in the product information. Also, that there is limited data regarding elderly patients above the age of 65 and this will also be reflected in the warning section of the product information of all testosterone-containing medicinal products.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of directive 2001/83/EC for testosterone-containing medicinal products.
- The Committee considered the studies that heightened concerns about the increased risk of cardiovascular events associated with testosterone therapy and available data submitted from clinical trials, observational studies, meta-analyses, post-marketing data and further published data.
- The Committee noted that the available data does not consistently show an increased risk of cardiovascular events during testosterone therapy.
- The PRAC noted that some of the studies have methodological limitations. Some studies show an increased risk while others do not suggest a risk and therefore have not corroborated the signal.
- The PRAC concluded that based on the overall currently available data, the suggested risk for cardiovascular events associated with the testosterone therapy remains a weak signal. The PRAC noted that others studies will become available.
- The Committee recognised the limited available information on testosterone therapy for age-related hypogonadism and also the lack of reference values. Further studies will be needed to provide relevant safety and efficacy data in this patient population.
- The Committee agreed, that it is justified to reflect in the product information of all testosterone-containing medicinal products the current knowledge on cardiovascular risks associated with testosterone therapy and recommended changes in section 4.1 (therapeutic

indications), section 4.4 (warnings and precautions for use) and section 4.8 (undesirable effects) of the Summary of Product Characteristics.

- The PRAC also concluded that there was the need for all MAHs to closely monitor cardiovascular risk and discuss the findings including venous thromboembolic events and possible mechanism(s) and usage pattern and adverse events in patients older than 65 years in the next PSUR.

In view of the above, the PRAC has recommended the variation to the terms of the Marketing Authorisations for testosterone-containing medicinal products (see Annex I), for which the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III and subject to the conditions set out in Annex IV of the PRAC recommendation.

The PRAC, as a consequence, concluded that the benefit-risk balance of testosterone-containing medicinal products remains favourable subject to the conditions to the marketing authorisations, and taking into account the amendments to the product information recommended.

2 – Detailed explanation of the scientific grounds for differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation.

However, the CMDh considered that an amendment was required in the package leaflet to improve clarity for patients that should tell their doctor if they have high blood pressure but also if they are being treated for high blood pressure. The wording was amended accordingly in section 2 of the Package Leaflet as set out in Annex III.

CMDh agreement

The CMDh, having considered the PRAC recommendation dated 9 October 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the variation of the marketing authorisations of testosterone containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.

The timetable for the implementation of the agreement is set out in Annex V.