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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 31 of Directive 2001/83/EC resulting from
pharmacovigilance data

Testosterone containing medicinal products

INN/active substance: testosterone

Procedure number: EMEA/H/A-31/1396

Note

Assessment report as adopted by the PRAC and considered by the CMDh with
all information of a commercially confidential nature deleted.



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1. Background information on the procedure

On 27 March 2014, further to evaluation of data resulting from pharmacovigilance, Estonia informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their concerns over cardiovascular risks associated with testosterone therapy (TT) and the need to perform an European review to evaluate the impact of the risk for cardiovascular events in the benefit-risk of testosterone-containing medicinal products in its approved indications.

Therefore, it was in the interested of the Union to refer the matter to the PRAC.

The Pharmacovigilance Risk Assessment Committee (PRAC) was requested to issue a recommendation on whether the marketing authorisations for testosterone-containing products should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

2.1. Introduction

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.

Hypogonadism is classified into primary testicular failure when due to a problem in the testicles and secondary testicular failure, when 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, delay of secondary sex characteristics and high pitched voice. The symptoms are less specific if the hypogonadism develops after puberty and are characterised by e.g. decreased sexual function, infertility, decreased energy, depressed mood, mild anaemia, reduced muscle bulk and strength, increased body fat and BMI (body mass index).

The major goal of testosterone replacing therapy (TT) is to achieve normal physiological testosterone levels to relieve symptoms of androgen deficiency, such as loss of libido, erectile dysfunction, changes in body composition (loss of body hair, low bone mineral density, gynaecomastia, reduced muscle strength and increased fat mass) 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.

Recent concerns have arisen about an increased risk of cardiovascular events namely increased risk of myocardial infarction in men who are receiving TT and who have pre-existing heart disease as

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.

suggested by a recent study by Finkle et al (2014)³. This study suggested a two fold increase in the relative risk 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 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 System⁴, 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 literature has identified a meta-analysis "Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomised trials" (Xu, 2013)⁵, which showed that testosterone increased the risk of cardiovascular-related events. These studies heightened concerns about the increased risk of cardiovascular events associated with testosterone therapy and led Estonia to initiate an European review.

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

2.2. Clinical aspects

In its assessment, the PRAC considered the data available from different sources: clinical trials, observational studies, meta-analyses, post-marketing data and further published data on the cardiovascular risks associated with testosterone therapy.

The PRAC also considered data from the European Pharmacovigilance database (Eudravigilance) and a drug utilisation study of the patterns of prescription of testosterone in the primary care setting in the United Kingdom.

A summary and discussion of relevant data is presented hereafter.

2.2.1. Safety

Studies that show an increased cardiovascular risk associated with testosterone therapy

Finkle et al., 2014³

This was a retrospective cohort study of the risk of acute non-fatal myocardial infarction (MI) following an initial TT prescription (N=55,593) in a large health-care database. The incidence rate of MI in the 90 days following the initial prescription (post-prescription interval) with the rate in the one year prior to the initial prescription (pre-prescription interval) (post/pre) was compared.

A comparison with post/pre rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil, N=167,279), and a comparison with prescription post/pre rates with the PDE5I post/pre rates was made and adjusting for potential confounders using doubly robust estimation.

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.

In men aged 65 years and older, the RR was 2.19 (1.27, 3.77) for TT prescription and 1.15 (0.83, 1.59) for PDE5I, and the RR for TT prescription relative to PDE5I was 1.90 (1.04, 3.49).

In men under the age of 65 years, excess risk was confined to those with a prior history of heart disease, with RRs of 2.90 (1.49, 5.62) for TT prescription and 1.40 (0.91, 2.14) for PDE5I, and a RR of 2.07 (1.05, 4.11).

The RRs for TT prescription compared to PDE5I were 2.07 (1.05, 4.11) for those under age 65 years with a history of heart disease and 0.91 (0.60, 1.37) for those without, and 1.90 (0.66, 5.50) for those aged 65 years and older with a history of heart disease, and 2.41 (1.12, 5.17) for those without.

These results show paradoxically that, in older men (aged 65 and older), those with a history of heart disease have a lower adverse effect size than those without history of heart disease.

The PRAC noted that the comparison of testosterone treatment with PDE5I is per se a limitation as the indication is not the same and furthermore PDE5I have a cardio-protective effect.

Overall, this study suggested a potential association of testosterone therapy with an increased risk of acute non-fatal myocardial infarction in older men and in younger men with pre-existing heart disease.

Vigen et al., 2013⁴

Reported on findings of a retrospective study using data from the US Veteran Administration (VA) health care system. The study population included a cohort of 8709 men with low serum testosterone who underwent coronary angiography between 2005 and 2011 and were followed until January 2012, achieving an average follow-up of 840 days. It was found that of the 8709 men with a total testosterone level lower than 300 ng/dl, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography.

When the T (N= 1223) and no T groups (N=7486) were compared there were some statistically significant differences and the no T group seemed sicker at the onset, since a large percentage of men in the no T group had obstructed coronary hypertension, congestive heart failure, prior acute myocardial infarction (AMI), and cardiovascular (CV) disease.

Raw data showed that death (9.1 vs 5.5 %), AMI (5.6 vs 1.9 %) and stroke (6.5 vs 2.7 %) were significantly increased in the no T group ($p < 0.0001$) compared to the T group. However after the application of a sophisticated statistical method (stabilised inverse probability of treatment weighting), the number of events were higher in the T group, with 19.9 % of events in the control group and 25.7 % in the TT group with an absolute risk difference of 5.8% (95% CI, -1.4% to 13.1%).

In Cox proportional hazards models adjusting for the presence of coronary artery disease, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, $P = 0.41$).

This study suggested that amongst a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes.

There were concerns that 1132 patients experiencing events were excluded because they were prescribed testosterone after the MI or stroke when these should have been included in the untreated group, increasing the events by 70%. Overall, the total number of events in the untreated group was 1587 (death 681, MI 420, stroke 486). Including the previously noted events would increase the

number of events in the untreated group by 71%, from 1587 to 2719. Consequently ignoring these events is expected to have a major effect on the outcome favouring the untreated group.

In addition, of the 1223 patients prescribed with testosterone therapy, 215 patients (17.6%) filled only 1 prescription. Such a group cannot be regarded as a long-term treatment. The treatment group had a significantly lower testosterone level, which by itself can increase the risk of CV events.

It was also noted that the authors did not adjust for baseline testosterone level and concomitant medicine.

This paper resulted in a number of responses (Traish et al., 2014; Jones et al., 2014; Morgentaler et al. 2014; Katz and Nadelberg., 2014; Morgentaler and Kacker 2014; Riche et al, 2014; Irwin 2014; Cappola 2014; Dhindsa et al., 2014), and afterward a response from the authors (Ho et al., 2014).

The authors clarified that, "*with regard to the 1132 excluded patients, there was an incorrect notation in the article that these were all patients prescribed testosterone. Rather, patients were excluded because coronary anatomy was categorized as other (n = 904) and for female sex (n = 100); and only 128 patients were excluded because they filled a testosterone prescription after myocardial infarction. Post hoc analysis including these 128 patients did not change the results (hazard ratio, 1.30; 95% CI, 1.06-1.60)*".

Xu et al., 2013

This was a systematic review and meta-analysis of placebo-controlled randomised trials of testosterone therapy among men lasting 12 or more weeks, reporting cardio-vascular-related events. A total of 27 trials were eligible including 2994, mainly older, men who experienced 180 cardiovascular-related events.

It was found that testosterone therapy increased the risk of a cardiovascular-related event (OR 1.54, 95%CI 1.09 to 2.18). The effect of testosterone therapy appeared to vary with the source of funding (p-value for interaction 0.03), but not with the baseline testosterone level (p-value for interaction 0.70). Furthermore, small studies which show that testosterone reduced cardiovascular (CV) events, are published while there is a lack of similar small studies where testosterone increased CV events.

A difference in cardiovascular risk with testosterone treatment between industry sponsored trials (no increased risk, OR 0.89, 95%CI 0.50 to 1.60) and non-industry sponsored trials (increased risk, OR 2.06, 95%CI 1.34 to 3.17) was noted, and likely due to systematic differences in the populations studied. Industry sponsored studies had younger, and likely healthier men with lower risk of cardiovascular outcomes. It should be noted that the funnel plot suggests some publication bias.

Basaria et al., 2010⁶

This study included community-dwelling fragile men, 65 years of age or older, with limitations in mobility and a total serum testosterone level of 100-350ng/dl (3.5-12.1nmol/l) or a free serum testosterone level of less than 50pg/ml (173pmol/l) who were randomly assigned to receive placebo gel or testosterone gel in supraphysiological dose daily during 6 months. This study was prematurely stopped following the data safety monitoring board recommendation for the study to stop due to significantly higher rate of adverse cardiovascular events in the testosterone group than in the placebo group.

⁶ Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363(2):109-22.

A total of 209 men (mean age, 74 years) were enrolled at the time the trial was terminated. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidaemia, and obesity among the participants. During the course of the study, the testosterone group had higher rates of cardiac, respiratory, and dermatologic events than the placebo group. A total of 23 subjects in the testosterone group, as compared to 5 in the placebo group, had cardiovascular-related adverse events. The relative risk of a cardiovascular-related adverse event remained constant throughout the 6-month treatment period. In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The authors cautioned that the small size of the trial and the unique population prevent broader inferences about the safety of testosterone therapy.

Studies that show no increased cardiovascular risk associated with testosterone therapy

Baillargeon et al., 2014⁷

A retrospective study using a 5% national sample of Medicare beneficiaries with the objective to examine the risk of myocardial infarction (MI) in a population-based cohort of older men receiving intramuscular testosterone was performed. A total of 6355 patients treated with at least 1 injection of testosterone between 1 January 1997, and 31 December 2005 and matched this cohort to 19065 testosterone non-users at a 1:3 ratio based on a composite MI prognostic score. Patients were followed until the end or until they lost coverage from Medicare, enrolled in a health maintenance organisation, experienced a MI, or died.

The results, in a Cox regression analysis adjusting for demographic and clinical characteristics, suggest that testosterone therapy was not associated with an increased risk of MI (hazard ratio [HR] = 0.84; 95% CI = 0.69-1.02). In this analysis, there was an interaction between receipt of testosterone and quartile of risk of MI (P = 0.023). For men in the highest quartile of the MI prognostic score, testosterone therapy was associated with a reduced risk of MI (HR = 0.69; 95% CI = 0.53-0.92), whereas there was no difference in risk for the first (HR = 1.20; 95% CI = 0.88-1.67), second (HR = 0.94; 95% CI = 0.69-1.30), and third quartiles (HR = 0.78; 95% CI = 0.59-1.01). They concluded that older men who were treated with intramuscular testosterone did not appear to have an increased risk of MI. For men with high MI risk, testosterone use was modestly protective against MI.

Corona et al., 2014⁸

An updated systematic review and meta-analysis of all placebo-controlled randomised clinical trials (RCTs) on the effect of testosterone on CV-related problems was performed. The authors chose the incidence of new major adverse cardiovascular event (MACE) as endpoints. Out of 2747 retrieved articles, 75 RCTs were analysed, including 3016 and 2448 patients in testosterone and placebo groups, respectively, and a mean duration of 34 weeks. Their analyses indicated that testosterone is not related to any increase in CV risk, even when composite or single adverse events were considered. In RCTs performed in subjects with metabolic derangements a protective effect of testosterone on CV risk was observed.

⁷ 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.

⁸ 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)

Tan et al., 2014⁹

The objective was to assess the association between testosterone therapy and Myocardial infarction (MI)-, or stroke among “low testosterone centre patients”. A retrospective analysis of patients that had MI and strokes pre and post testosterone therapy was performed. Data was extracted from electronic health records (Advance MD) of the multi-site Low T Centres across the United States. Altogether 40 Centres were included in the study.

Overall, 39937 patients were seen between the years 2009-2014 and approximately 50% met criteria for treatment. Of the treated patients, there were 4 non-fatal MI and 2 probable fatal MI; and rate of new MI was 30 per 100,000. There were 46 patients with pre therapy MI of which none had adverse outcomes after testosterone. Of the treated patients, there were 2 cases of stroke; and rate of new stroke was 10 per 100,000. There were 12 patients with pre-therapy stroke and none had adverse outcomes after testosterone. The risks for new MI and stroke were compared to the Kaiser Permanente and Northern Manhattan Registry which was 208 per 100,000 and 93 per 100,000 respectively. Rate ratio (RR) for MI in testosterone treated patients is 0.14 (C.I. 0.098 to 0.211, $p < 0.0001$) whereas for strokes is 0.107 (C.I. 0.06 to 0.21, $p < 0.0001$). The study suggests that carefully monitored testosterone treated patients have 7 and 9 times lower risk of developing MI and strokes respectively as compared to similar community data sets.

RHYME (Registry of Hypogonadism in Men)

This was a study performed in 6 European countries by the New England Research Institutes (NERI). The primary aim of RHYME was to examine the association between testosterone therapy (over at least 2 years) and prostate health outcomes in men with clinically diagnosed hypogonadism (HG). A secondary aim of the registry was to examine the association between testosterone therapy (TT) and other health outcomes, including cardiovascular events determined from the medical record.

The conclusions of this report on CV events suggest that men who experienced new onset CV events during the period of follow up have most of the usual risk factors associated with increased CV risk including older age, higher BMI and waist circumference, past or present smoking, elevated blood pressure and cholesterol, history of CVD and related prescription medication use.

Additional data on cardiovascular risk associated with testosterone

Most of the clinical trials presented by the MAHs, did not assess cardiovascular events (CV) as a primary outcome, as the data were mostly phase I, II and III pivotal studies of the development programme to evaluate the efficacy and pharmacokinetics of the relevant testosterone containing products.

These data have limitations as no predefined diagnostic criteria and screening methods for CV diseases were overall considered. In many of the clinical trials, the participants also had a number of co-morbidities and co-medications and many of the studies did not include a placebo group, and in a few, which had a placebo group, there seemed to be no significant differences between groups with regard to CV events.

The analysis of post-marketing data presented by the MAHs, does not allow any conclusion about testosterone causality for CV events to be draw.

⁹ 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>

Overall, data from clinical trials and from post-marketing spontaneous reports do not contribute to an association of testosterone therapy and cardiovascular events.

Shores et al., 2012¹⁰

This was an observational, retrospective cohort study based on data obtained from seven Veterans Affairs (VA) medical centres in the Northwest United States. The study cohort included 1031 male veterans, aged 40 years and older, who had low total testosterone (≤ 250 ng/dl) and no history of prostate cancer.

Testosterone treatment was initiated in 398 men (39%) during routine clinical care. The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men ($p < 0.0001$) with a mortality rate of 3.4 deaths per 100 person-years for testosterone-treated men and 5.7 deaths per 100 person-years in men not treated with testosterone. After adjustment for relevant risk factors including age, BMI, testosterone level, co-morbidity, diabetes, and coronary heart disease, testosterone treatment was associated with a decreased risk of death (HR 0.61; 95%CI 0.42 to 0.88).

No significant effect modification was found for age, diabetes, or coronary heart disease. The study results suggest that in a cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment. These results should be interpreted cautiously due to residual confounding as a potential source of bias. The authors concluded that large, randomized clinical trials are needed to better characterize the health effects of testosterone treatment in older men with low testosterone levels.

Hildreth et al. (2013)¹¹

The TEAM "The Testosterone Supplementation and Exercise in Elderly Men" Study studied the effects of T supplementation with and without progressive resistance training (PRT) on functional performance, strength, and body composition. A total of 167 generally healthy community-dwelling older men (66 ± 5 years) with low-normal baseline total T levels (200-350 ng/dl) were recruited. Subjects were randomized to placebo or transdermal T gel [2 doses targeting either a lower (400-550 ng/dl) or higher (600-1000 ng/dl) T range] and to either PRT or no exercise for 12 months.

A total of 143 men completed the study. At 12 months, total T was 528 ± 287 ng/dl in subjects receiving any T and 287 ± 65 ng/dl in the placebo group. In the PRT group, function and strength were not different between T- and placebo-treated subjects, despite greater improvements in fat mass ($P = 0.04$) and fat-free mass ($P = 0.01$) with T. In the non-PRT group, T did not improve function but improved fat mass ($P = 0.005$), fat-free mass ($P = 0.03$), and upper body strength ($P = 0.03$) compared with placebo. There were fewer cardiovascular events in the T-treated groups compared with placebo.

The authors concluded that testosterone supplementation was well tolerated and improved body composition but had no effect on functional performance. Testosterone supplementation improved upper body strength only in non-exercisers compared with placebo.

The study found fewer cardiovascular events in the testosterone treated group compared to placebo (3 in the testosterone group versus 10 in the placebo). However, it should be noted that cardiovascular events were not included as either primary or secondary outcomes.

¹⁰ Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab.* 2012;97(6):2050-8.

¹¹ Hildreth KL, Barry DW, Moreau KL, Vande Griend J, Meacham RB, Nakamura T, Wolfe P, Kohrt WM, Ruscin 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.

Ongoing studies

The PRAC identified five ongoing studies for which results will become available by end 2015. These studies are the following:

- (ClinicalTrials.gov ID# NCT00799617) - The Testosterone Trial in Older Men.
- (NIH Grant ID#NCT01813201)- Benefit of the Treatment With Testosterone in Chronic Heart Failure Testosterone Deficiency Subjects (TIC).
- (NIH Grant ID#5R01AG042845-02) medical database observational study that is being conducted at the University of North Carolina, from which results on the potential relationship between TT and MACE are expected.
- (NIH Grant ID# 5R01AG042921-02)- A medical claims database study being conducted by the Kaiser Foundation that will evaluate CV events in men undergoing TRT.
- (NIH Grant ID#5R01AG042934-02)- An epidemiological study being conducted by the Seattle Institute for Biomedical/Clinical Research evaluating the incidence/severity of CV events (including MACEs) from >480,000 men (including >160,000 men who were administered TRT between 2001 and 2012).

MAHs are expected to reflect the findings of these studies in the next Period Safety Update Report (PSUR) for which the common data lock point (DLP) to all testosterone-containing medicinal products will be 31 December 2015.

Data on prescribing testosterone in the primary care setting in the United Kingdom

The presented study aimed to describe the extent and patterns of prescription of testosterone in the primary care setting in the United Kingdom (UK) databases. The objective of the study was to estimate the prevalence of testosterone use in males from 1990 to Q1 2013. The study results showed an increase in prescription of testosterone in the period 1995-2012. However, at the same time it is reasonable to assume that the percentage of elderly in the total population also increased. As this increase is not presented in the data, it is very difficult to assess, if the increased usage, could also be explained by the increased number of elderly. Furthermore, as the study only regards exposure to testosterone in the UK, the findings cannot be extrapolated to other EU Member States. The study confirmed, however that patients receiving testosterone treatment for hypogonadism, were older and seemed to have more cardiac related comorbidities.

2.2.2. Efficacy

The major goal of testosterone treatment is to achieve normal physiological testosterone levels to relieve symptoms of androgen deficiency, such as loss of libido, erectile dysfunction, changes in body composition and psychological impairment. Testosterone has demonstrated beneficial effects on osteoporosis, insulin resistance, and other parameters of metabolic syndrome (MetS).

The European Association of Urology, in its last guideline on male hypogonadism, lists metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and insulin resistance as signs and symptoms suggestive of androgen deficiency (Dohle et al., European Association of Urology 2012).

Several studies have been published supporting the beneficial effects of testosterone in body composition, anthropometry and metabolic parameters. More recent studies include *Hildreth et al.* (2013) above, *Francomano et al.* (2014)¹² and *Yassin et al.* (2013)¹³.

The PRAC 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 on this patient population.

2.2.3. Discussion on available data

Overall, data available on the cardiovascular risks associated with testosterone therapy (TT) come mainly from observational studies. The findings of the observational studies are however, per se inconsistent with regards the association of TT and cardiovascular risks, with some of these studies suggesting an increased risk of cardiovascular events (i.e. *Finkle et al.*, 2014³; *Vigen et al.*, 2013⁴) while others suggesting no risk (e.g. *Baillargeon et al.*, 2014⁷; *Tan et al.*, 2014⁹). The same is noted with findings from systematic review and meta-analyses of data from randomised clinical trials, e.g. *Xu et al.*, 2013⁵ ad *Corona et al.*, 2014⁸.

The findings of *Finkle et al.* (2014) and *Vigen et al.* (2013), suggested a two fold increase in the relative risk of myocardial infarctions (MI) in the 90 days after starting TT in men who had heart disease compared to the year before and higher frequency of death and cardiovascular events in men who had documented coronary artery disease and who were on TT. Findings of other observational studies such as *Baillargeon et al.*, 2014; *Tan et al.*, 2014 suggest no increased risk of myocardial infarction (MI) in older men who were on TT and lower risk of developing MI and strokes when compared to similar community data sets when carefully monitored.

The systematic reviews and meta-analyses of randomised clinical trials seemed to suggest that TT increased the risk of cardiovascular events (*Xu et al.*, 2013)⁵ while others looking at major adverse cardiovascular events suggest that testosterone is not related to any increase in cardiovascular risk (*Corona et al.*, 2014)⁸.

An additional study (*Basaria et al.*, 2010)⁶ performed in patients older the 65 years with limitation in mobility and assigned to receive placebo or testosterone gel suggested an increased risk of cardiovascular events which justified an earlier termination of the study. 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.

Overall it is acknowledged that the data available has methodological limitations (e.g. retrospective studies use databases which may not be able to capture all relevant covariates for cardiovascular risks, limited in scope and size) which leads to findings which are inconclusive with regards the association of TT and cardiovascular risks. Therefore, the PRAC agreed that the suggested risk for cardiovascular events associated with TT remains a weak signal. The PRAC noted that others studies will become

¹² Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol* 2014; 2014: 527470a.
Francomano D, Bruzziches R, Barbaro G, Lenzi A, Aversa A. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. *J Endocrinol Invest* DOI 10.1007/s40618-014-0066-9b.

¹³ Yassin A, Doros G. Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss. *Clinical obesity*. 2013; 3(3-4): 73-83.

available and the MAHs are expected to discuss their findings in the next Periodic Safety Update Report (PSUR).

The PRAC recognised the benefits of testosterone therapy in the approved indication of hypogonadism.

The PRAC noted that in the labelling of some products, the indication clearly refers that testosterone deficiency has to be confirmed by clinical features and biochemical tests, while in other products this additional guidance is lacking. This guidance is also in accordance with the guideline of Endocrine Society. Moreover, *Corona et al., 2014* stressed the importance of testosterone being used when there is demonstrated hormone deficiency and associated symptomatology. Therefore, the PRAC agreed that the product information for all testosterone products affected by the review should refer clearly that the diagnosis of hypogonadism is to be confirmed through both clinical features and biochemical testing. Consequently amendments to section 4.1 of the Summary of Products Characteristics (SmPC) were agreed (please see section 4. below).

It is known that testosterone, as well as other androgens and anabolic steroids, are to 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. Information in this regard is already included in the labelling of some products. In order to ensure consistency, the PRAC recommended that a common warning to patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, that testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure and that in such case, treatment must be stopped immediately, should be included.

In addition, the PRAC recommended that laboratory parameters be monitored regularly when on long term treatment. Haemoglobin, haematocrit, liver function tests and lipid profile were added as warnings as well as the use with caution in men with hypertension. The undesirable effects section of the SmPC also reflects the common increase of haematocrit, red blood cell count and haemoglobin associated with testosterone therapy.

Moreover, the warning that the levels of testosterone should be measured not only at baseline but at regular intervals during the treatment to ensure maintenance of eugonadal testosterone levels, hence measuring the efficacy of the replacement therapy, was already part of the labelling of some products. The PRAC agreed that all products should have this information. In this regard the PRAC recognised the limited available information on testosterone therapy for age-related hypogonadism particularly in patients older than 65 years of age and the lack of age specific testosterone reference values. Further studies will be needed to provide relevant safety and efficacy data on this patient population.

All MAHs were also requested to monitor cardiovascular risk (including literature, clinical trials and all other relevant data) and discuss the findings in the next PSUR. In addition the next PSUR should include a separate section regarding VTE (including DVT and PE). This section shall also include literature regarding testosterone and VTE (including case reports) and the spontaneous reports shall be subject of a general discussion of the cases, and include all relevant information, e.g. time to onset (when available), haematocrit/haemoglobin level (when available), indication, age, confounding factors. Furthermore, according to the findings, the MAH should discuss in the next PSUR the possible mechanism for the association between cardiovascular/VTE event and testosterone level (and whether low or high level compared to eugonadal level may contribute to the increased risk) and finally if the information should be included in the product information.

The MAHs are also requested to discuss in the next PSUR the usage in patients older than 65 years of age, taking into account the naturally lower level of testosterone in this age group. When discussing

the ADRs in this group the MAH should consider if the pattern of ADRs is comparable to other age groups or if some ADRs have a notably higher frequency.

The next PSUR should be submitted in accordance with the common data lock point (DLP) for all testosterone-containing medicinal products (31 December 2015). The EURD list will be amended accordingly.

3. Overall discussion and benefit/risk assessment

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

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-analyses 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., 2014; Corona et al., 2014; Tan et al., 2014, Hildreth et al., 2013*), 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 values. 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 cell proliferation, which theoretically could increase the risk of thromboembolic events. Given the 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 data lock point (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 are 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.

4. Product information

As discussed above, the PRAC considered that updates to the product information would be necessary in order to ensure that the potential cardiovascular risks associated with testosterone use are addressed in all products approved.

These changes include amendments to sections 4.1, 4.4 and 4.8 of the Summary of Product Characteristics as follows. These changes are reflected accordingly in the Package leaflet.

Summary of Product Characteristics

Section 4.1 “Therapeutic indications”

Testosterone replacement therapy for male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

[...]

Section 4.4 "Special Warnings and Precautions for Use"

[...]

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.

Testosterone may cause a rise in blood pressure and <name of product> should be used with caution in men with hypertension.

Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin, and haematocrit, liver function tests and lipid profile.

There is limited experience on the safety and efficacy of the use of <name of product> in patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

[...]

Section 4.8 "Undesirable effects"

[...]

Haematocrit increased, Red blood cell count increased, Haemoglobin increased
Frequency common.

[...]

Package Leaflet

[...]

1. What <name of product> is and what it is used for

<name of product> is used in adult men for testosterone replacement to treat various health problems caused by a lack of testosterone (male hypogonadism). This should be confirmed by two separate blood testosterone measurements and also include clinical symptoms such as:

impotence

infertility

low sex drive

tiredness

depressive moods

bone loss caused by low hormone levels

[...]

2. What you need to know before you take <name of product>

[...]

If you are suffering from severe heart, liver or kidney disease, treatment with <name of product> may cause severe complications in the form of water retention in your body sometimes accompanied by (congestive) heart failure.

The following blood checks should be carried out by your doctor before and during the treatment: testosterone blood level, full blood count.

Tell your doctor if you have high blood pressure as testosterone may cause a rise in blood pressure
[...]

4. Possible side effects

Frequency common: Increase in red blood cell count, haematocrit (percentage of red blood cells in blood) and haemoglobin (the component of red blood cells that carries oxygen), identified by periodic blood tests.

[...]

5. Conclusion and grounds for the 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, 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 Committee, 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.