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PRAC review does not confirm increase in heart problems with testosterone medicines

Committee recommends medicines can continue to be given for their authorised uses

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed an EU-wide review of testosterone-containing medicines following concerns over serious side effects on the heart and blood vessels, including heart attack. The PRAC review did not find consistent evidence that the use of testosterone in men who do not produce enough testosterone (a condition known as hypogonadism) increases the risk of heart problems. The committee considered that the benefits of testosterone continue to outweigh its risks but recommended that testosterone-containing medicines should only be used where lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests.

The evidence about the risks of serious side effects on the heart of these medicines is inconsistent. While some studies including three recently published studies^{1,2,3} did suggest an increased risk of heart problems in men using testosterone compared with men not taking it, these studies had some limitations and others did not confirm this risk.^{4,5} The PRAC also noted that the lack of testosterone itself could increase the risk of heart problems. The PRAC therefore recommended that testosterone-containing medicines should only be used if the lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests. The EU product information for all testosterone-containing medicines should be updated to include this recommendation as well as warnings against use in men suffering from severe heart, liver or kidney problems. The limited data on safety and effectiveness in patients over 65 years of age as well as the fact that testosterone levels decrease with age and that age-specific testosterone reference values do not exist will be highlighted in the product information.

¹ 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.

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):1829-1836.

³ Finkle et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One.* 2014 Jan 29;9(1):e85805.

⁴ 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.

⁵ Corona G, Maseroli E, Rastrelli G, Isidori A, Mannucci E, Maggi M. Cardiovascular risk associated with testosterone boosting medications: a systematic review and meta-analysis. *Exp Opin Drug Safety* 2014 (Posted online on August 19, 2014. (doi:10.1517/14740338.2014.950653)



The safety of testosterone medicines should continue to be monitored. In particular, a number of studies are still ongoing and their results will be considered in future regular benefit-risk assessments for these medicines.

The PRAC recommendation will now be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) which will adopt a final position.

More about the medicine

Testosterone-containing medicines have been authorised in all EU Member States via national procedures under various trade names. They are available as various formulations such as oral capsules, implants to be injected under the skin and as patches, gels or solutions to be applied to the skin.

Testosterone-containing medicines are used to replace testosterone in men with hypogonadism. The use of testosterone in healthy older men is not an authorised use in the EU.

Testosterone is a hormone, known as an androgen, responsible for the development of reproductive function in men. In men with hypogonadism, testosterone levels are abnormally low, affecting normal sexual development. Testosterone-containing medicines work by replacing the missing testosterone, helping to restore normal testosterone levels to ensure normal sexual development in men. Possible signs and symptoms include incomplete sexual development, decreased sexual function, infertility, fatigue, depressed mood, mild anaemia, reduced muscle bulk and strength and increased body fat.

More about the procedure

The review of testosterone was initiated on 27 March 2014 at the request of Estonia, under Article 31 of Directive 2001/83/EC. It follows concerns over reports about side effects of these medicines on the heart.^{2,3}

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As testosterone-containing medicines are all authorised nationally, the PRAC recommendation will now be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a regulatory body representing EU Member States, and is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

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