

EUROPEAN MEDICINES AGENCY TESTOSTERONE UPDATE

The European Medicines Agency (EMA) released a statement regarding the use of Testosterone Replacement Therapy in Europe, titled ‘No consistent evidence of an increased risk of heart problems with testosterone medicines’

Please find the statement attached, which was released on 21 November 2014.

Contact

Michael Kotsanis, Chief Executive Officer: 03 8379 0100

About Acrux

- Acrux is an Australian drug delivery company, developing and commercialising a range of patient-preferred, patented pharmaceutical products for global markets, using its innovative technology to administer drugs through the skin.
- The Acrux technology, used in marketed products including Axiron®, Evamist® and Recuvyra™, is based on a fast-drying, small volume, accurately dosed solution, containing penetration enhancers, that when applied topically, deposits drug through the skin for long acting delivery.
- Acrux has three products marketed by licensees in the USA, three products approved in Europe, and further products at earlier stages of development



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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No consistent evidence of an increased risk of heart problems with testosterone medicines

The CMDh¹, a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.

The CMDh position follows a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) which looked at the risk of serious problems affecting the heart and circulation, particularly heart attacks, in men treated with these medicines. The review was started because of some recent studies suggesting an increase in heart problems in men using testosterone, compared with men not using it. The PRAC considered these studies along with available data from other studies and analyses, and information on safety collected since marketing, and found that the evidence regarding the risk of heart problems was inconsistent: some studies suggested increased risk, while others did not, and some of the studies had problems with the design that limited the conclusions that could be drawn from them. The PRAC also noted that the lack of testosterone itself could increase the risk of heart problems.

The PRAC recommended updating the product information in line with the latest evidence and to provide warnings about those who might be at increased risk of heart problems. The product information should make it clear that testosterone should only be used when an abnormally low level of the hormone has been confirmed by signs and symptoms and appropriate laboratory tests. Testosterone levels naturally fall somewhat with age, but restoration of these levels in healthy older men is not an authorised use of the medicine in the EU. The PRAC further considered that the risks of effects on the heart and circulation, and any potential mechanisms for such effects should continue to be monitored, and information from ongoing studies should be provided as part of the next regular safety review (to which these medicines, like all medicines in the EU, are subject).

The CMDh has endorsed the PRAC recommendations by consensus and they will now be directly implemented according to an agreed timetable by the Member States where the medicines are authorised.

¹ The Coordination Group for Mutual Recognition and Decentralised Procedures – Human



Information to patients

- Testosterone is a hormone responsible for normal sexual development and function in men. Medicines containing testosterone are licensed in the EU to treat men with abnormally low levels of the hormone (hypogonadism).
- Some recent studies have suggested that using testosterone may increase a man's risk of heart attacks or other serious effects on the heart and circulation. However, an in-depth review did not find any conclusive evidence that this was the case.
- As a precaution, the product information for these medicines will be updated with the latest information on the risks together with some additional warnings for safe use, and the safety of the medicines will continue to be closely monitored.
- Patients who are prescribed testosterone should remind their doctors if they are being treated for high blood pressure, as testosterone can also increase blood pressure.
- The product information will also be amended to make it clear that these medicines should only be given to men in whom both signs and symptoms and laboratory tests confirm abnormally low levels of testosterone.
- There is not much information on the use of testosterone medicines in men over 65 years of age. The level of testosterone falls naturally with age and testosterone-containing medicines are not approved in the EU for use to boost testosterone levels in healthy older men.
- Patients who have any concerns about their treatment should discuss them with their doctor or pharmacist.

Information to healthcare professionals

Testosterone-containing medicines are licensed in the EU for the treatment of male hypogonadism. The benefit-risk balance of these medicines has been reviewed following recent published evidence pointing to an increased risk of cardiovascular events, particularly myocardial infarction, in men treated with testosterone.

- Although some studies show an increased risk of cardiovascular events in men treated with testosterone, findings in the literature do not show this consistently. Taking all the data into account, the signal for an increased cardiovascular risk associated with the use of testosterone remains weak and inconclusive.
- Testosterone replacement therapy should only be given when deficiency of the hormone has been confirmed by clinical features and biochemical tests. Testosterone levels should then be monitored regularly during treatment. Haemoglobin, haematocrit, liver function and blood lipid profile should also be monitored regularly.
- 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 a case, treatment must be stopped immediately.
- Caution is also advised in patients with pre-existing hypertension, since testosterone may cause an increase in blood pressure.
- There is limited experience on the safety and efficacy of the use of these medicines in patients over 65 years of age. It should be borne in mind that physiological testosterone levels decrease

somewhat with age, though there is no current consensus on appropriate age-specific testosterone reference values, and use to boost these levels in healthy older men is not an authorised use in the EU.

The changes to the product information for testosterone medicines are based on a PRAC review of data available from clinical trials, observational studies, meta-analyses, post-marketing data and further published data on the cardiovascular risks associated with testosterone therapy.

- Some recent studies have shown an increased risk of cardiovascular events in men treated with testosterone. In particular, 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.¹⁻³
- However, other findings⁴⁻⁷ do not provide evidence of an association between testosterone and cardiovascular events, and data from a multinational observational registry study (RHYME) looking at prostate health outcomes in men treated with testosterone for over 2 years also indicate cardiovascular events within the anticipated range.
- The cardiovascular safety of testosterone medicines will continue to be monitored and the findings of ongoing studies will be reflected in the next regular benefit-risk assessments when available.
- Relevant safety and efficacy data in patients with age-related hypogonadism and established physiological reference values in older patients are lacking, and further studies are needed.

References.

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3. Xu L, Freeman G, Cowling BJ, *et al.* Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013; 11: 108.
4. Baillargeon J, Urban RJ, Kuo Y-F, *et al.* Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother* 2014; 48: 1138-44.
5. Corona G, Maseroli E, Rastrelli G, *et al.* Cardiovascular risk associated with testosterone boosting medications: a systematic review and metaanalysis. *Expert Opin Drug Safety* 2014; 13: 1327-51.
6. 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), p. 238, abstract #1353. Available at: <https://www.aace.com/files/late-breaking-abstracts-2014.pdf>
7. Hildreth KL, Barry DW, Moreau KL, *et al.* Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab* 2013; 98: 1891-1900.

More about the medicine

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-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 is a hormone, known as an androgen, responsible for the development and maintenance of reproductive function and sexual characteristics in men. In men with hypogonadism, testosterone levels are abnormally low, affecting normal sexual development and function. Testosterone-containing medicines work by replacing the missing testosterone, helping to restore normal testosterone levels to ensure normal sexual development and function 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.

A review of these data was first conducted by the PRAC, the EMA's Committee responsible for the evaluation of safety issues for human medicines. The PRAC recommendations were sent to the CMDh, which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, it will now be directly implemented according to an agreed timetable by the Member States where the medicines are authorised.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu