FDA TESTOSTERONE UPDATE

Acrux (ASX: ACR) today confirmed that the Food and Drug Administration (FDA) has released a statement regarding the use of Testosterone Replacement Therapy in the US, titled 'FDA Cautions About Using Testosterone Products for Low Testosterone Due to Aging; Requires Labeling Change to Inform of Possible Increased Risk of Heart Attack And Stroke".

Acrux confirms that Lilly is liaising with the FDA and will continue to work closely with the agency in the best interests of men who use testosterone therapy. Based on the FDA's statement, the agency is requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Health care professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy.

Please find the statement attached, which was released on 4th March 2015 AEDT.

Acrux will be addressing shareholder and analyst questions later this morning and dial-in details for this call will follow shortly.

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

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.

Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism. Examples of these disorders include failure of the testicles to produce testosterone because of genetic problems, or damage from chemotherapy or infection. However, FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.

In addition, based on the available evidence from published studies and expert input from an Advisory Committee meeting, FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.

Based on our findings, we are requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Health care professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy. We are

also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. We are encouraging these manufacturers to work together on a clinical trial, but they are allowed to work separately if they so choose.

Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as:

- Chest pain
- Shortness of breath or trouble breathing
- Weakness in one part or one side of the body
- Slurred speech

A list of FDA-approved testosterone products can be found by searching for "testosterone" at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

We urge health care professionals and patients to report side effects involving testosterone products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about testosterone

- FDA has approved testosterone products to replace testosterone in men who have low testosterone levels associated with certain medical conditions. Examples of these conditions include:
  - Failure of the testicles to produce testosterone because of genetic problems or because of damage from chemotherapy
  - Problems with the pituitary gland or part of the brain called the hypothalamus that control the production of testosterone by the testicles
- FDA-approved testosterone formulations include gels, solution, skin patch, intramuscular injection, pellets implanted under the skin, and a buccal system applied to the upper gum or inner cheek.
- Testosterone is a hormone essential for the growth and development of male sex organs and maintenance of secondary male characteristics, such as facial hair.
- In the past 5 years, the use of testosterone replacement therapy has increased significantly, from 1.3 million patients in 2009 to 2.3 million patients in 2013 receiving a prescription for a testosterone product. Currently, approximately 70 percent of men who receive testosterone prescriptions through retail pharmacies are between 40 and 64 years old.[1] The most common diagnostic code associated with testosterone therapy is the non-specific diagnosis of "testicular hypofunction, not elsewhere classified."[2]
- A diagnosis of hypogonadism requires laboratory evidence of low testosterone levels measured on at least two separate mornings. However, in one health plan database, approximately 20 percent of men who received testosterone prescriptions had no insurance claims for laboratory testing of testosterone levels.[3]

- A list of FDA-approved testosterone products can be found by searching for "testosterone" at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

Additional Information for Patients

- Testosterone replacement therapy is only approved for men who have low levels of testosterone related to certain medical conditions. Examples of these conditions include genetic problems, and chemotherapy or infections that have damaged the testicles.
- The benefit and safety of testosterone have not been established in men who have low testosterone levels for no reason other than age, even if symptoms seem related to low testosterone. Testosterone levels can decrease naturally as men age, and sometimes these levels can become lower than the normal range seen in young, healthy men. Aging men can also experience signs and symptoms such as decreases in energy level and problems with sexual function, but it is uncertain whether these are caused by the lowered testosterone levels or due to normal aging. Therefore, the need to replace testosterone in these aging men is unclear.
- Heart attacks and strokes have been reported with testosterone treatment. Seek medical attention right away if you have symptoms of a heart attack or stroke, such as:
    - Chest pain
    - Shortness of breath or trouble breathing
    - Weakness in one part or one side of the body
    - Slurred speech
- Read the patient Medication Guide or patient information leaflet you get along with your prescription testosterone product. These materials explain the benefits and risks associated with testosterone use.
- Talk to your health care professional if you have questions or concerns about testosterone treatment.
- A list of FDA-approved testosterone products can be found by searching for "testosterone" at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
- Report side effects from testosterone treatment to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Testosterone replacement therapy is approved for use only in men with primary or secondary hypogonadism resulting from certain medical conditions.
- The safety and efficacy of testosterone replacement therapy for age-related hypogonadism have not been established.
- Before initiating testosterone replacement therapy, ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing. Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range. Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.

- For each patient, weigh the potential increased risk of major adverse cardiovascular outcomes and other risks of testosterone replacement therapy against the potential benefits of treating hypogonadism.
- Inform patients of the potential increased cardiovascular risk associated with testosterone replacement therapy.
- Encourage patients to read the patient Medication Guide or patient information leaflet they receive with their testosterone prescriptions.
- Report adverse events involving testosterone treatment to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

FDA reviewed five observational studies[4-8] and two meta-analyses of placebo-controlled trials[9,10] to examine the risk of cardiovascular events associated with testosterone replacement therapy (TRT). The five observational studies were retrospective cohort studies that reported conflicting results. Two of these studies found statistically significant cardiovascular harm with TRT (Vigen and Finkle), [4-5] two studies found a statistically significant mortality benefit with TRT (Shores and Muraleedharan), [6-7] and one study was inconclusive (Baillargeon).[8]

The Vigen study evaluated male veterans who underwent angiography and had low testosterone concentrations. On average, testosterone-treated men were 64 years old and untreated men were 61 years old. This study found an increased risk with TRT compared to no TRT for the composite cardiovascular outcome of myocardial infarction, stroke, and death (Hazard Ratio [HR]=1.29, 95% Confidence Interval [CI]: 1.04-1.58).[4]

The Finkle study evaluated TRT users in a large claims database. The men included in this study were on average 54 years old. This study found an increased risk of non-fatal myocardial infarction during the 90 days following an initial prescription for TRT compared to the pre-TRT period (Relative Risk [RR]=1.36, 95% CI: 1.03-1.81).[5]

The Shores study evaluated a population of male veterans older than 40 years of age with low testosterone and found a decreased risk of all-cause mortality with TRT compared to no TRT (HR=0.61, 95% CI: 0.42-0.88).[6]

The Muraleedharan study evaluated men with type 2 diabetes in the United Kingdom. The main analysis assessed mortality in men with low serum testosterone concentrations compared to men with normal serum testosterone concentrations. Mortality was also assessed in a subgroup analysis of treated and untreated men with low serum testosterone; an increased risk of all-cause mortality in men with no TRT compared to those on TRT was found (HR=2.30, 95% CI: 1.30-3.90).[7]

Finally, the Baillargeon study evaluated men older than 65 years of age enrolled in Medicare and found no overall increase in risk of hospitalization for myocardial

infarction when comparing those treated with TRT to those receiving no TRT (HR=0.84, 95% CI: 0.69-1.02).[8]

The Xu meta-analysis involved 27 published, randomized, placebo-controlled trials representing 2,994 mostly middle-aged and older male participants (1,773 treated with testosterone and 1,261 treated with placebo) who reported 180 cardiovascular-related adverse events.[9] This study found that testosterone therapy was associated with an increased risk of adverse cardiovascular events (Odds Ratio [OR]=1.5, 95% CI: 1.1-2.1); however, methodological issues limit conclusions. These limitations include inconsistent and incomplete reporting of adverse events; substantial clinical heterogeneity in the design and conduct of the component trials and the types of cardiovascular outcomes included in the analyses; potential bias resulting from selection of component trials; and variable quality of the trials, particularly with regard to ascertainment of cardiovascular safety outcomes and balance in cardiovascular risk factors and discontinuation rates across study arms.

The Corona meta-analysis involved 26 published, randomized, controlled trials, 20 of which were also included in the Xu meta-analysis. The included studies represented 3,236 men (1,895 men treated with testosterone, 1,341 men treated with placebo) who reported 51 major adverse cardiovascular events, defined as cardiovascular death, non-fatal myocardial infarction or stroke, and serious acute coronary syndromes or heart failure.[10] This study did not find a statistically significant increased risk of these cardiovascular events associated with testosterone treatment. Similar to the first meta-analysis, this study had methodological issues that limit conclusions. These issues include incomplete adverse event reporting in the published trials, clinical trial heterogeneity, possible treatment arm imbalances in cardiac risk factors, high or unbalanced discontinuation rates in some component trials, and the potential for bias in trial selection and interpretation of reported adverse events.

The five observational studies and the Xu meta-analysis were discussed at a joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 17, 2014. Based on these findings, the advisory committee members were in general agreement that the signal of cardiovascular risk is weak and that only a prospective, well-controlled clinical trial could determine whether testosterone causes cardiovascular harm. The Corona study was recently published and could not be reviewed in time to be presented at the Advisory Committee meeting; however, we have reviewed the study and factored its findings into our overall assessment.

For complete reviews, background information, and minutes of the September 17, 2014, Advisory Committee meeting, click here.

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