Testosterone Products — Drug Safety Communication Update

- On March 3, 2015, the FDA announced that manufacturers of all approved testosterone products are required to change their labeling to clarify the approved uses of these medications. The FDA also concluded that there is a possible increased cardiovascular (CV) risk associated with testosterone use; product labels will be updated to reflect this safety concern.

- Testosterone replacement therapy (TRT) is FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure to produce testosterone due to genetics, chemotherapy, or issues with the hypothalamus and pituitary gland.

- FDA-approved testosterone formulations include topical gel (eg, AndroGel®), topical solution (Axiron®), transdermal patch (eg, Androderm®), buccal system (Striant®), injection (eg, testosterone cypionate), nasal gel (Natesto™), and an implantable pellet (Testopel®).

- TRT should only be prescribed for men with low testosterone levels caused by certain medical conditions confirmed by laboratory tests. The benefit and safety of TRT have not been established for the treatment of low testosterone levels due to aging, even if symptoms seem related to low testosterone levels.

  — Before initiating TRT, health care providers should ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing. Serum testosterone concentrations should be measured on at least two separate mornings and fall consistently below the normal range. Avoid measuring testosterone concentrations later in the day, when levels can be low even in men who do not have hypogonadism.

- The 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.

- Healthcare providers should make patients aware of a possible CV risk when deciding whether to start or continue a patient on TRT. Symptoms of a myocardial infarction (MI) or stroke include chest pain, shortness of breath, weakness in one part or side of the body, and slurred speech.

- The FDA communication is based on data from five observational studies and two meta-analyses that examined the risk of CV events associated with testosterone therapy. The five observational studies were retrospective cohort studies that reported conflicting results. Two of these studies found statistically significant CV harm with TRT (Vigen and Finkle), two studies found a statistically significant mortality benefit with TRT (Shores and Muraleedharan), and one study was inconclusive (Baillargeon).

  — The Vigen study evaluated male veterans who underwent angiography and had low testosterone concentrations. This study found an increased risk with TRT vs. no TRT for the composite CV outcome of MI, stroke and death (hazard ratio [HR] = 1.29, 95% CI: 1.04-1.58).
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— The Finkle study evaluated TRT users in a large claims database. This study found an increased risk of non-fatal MI during the 90 days following an initial prescription for TRT vs. the pre-TRT period (relative risk [RR] = 1.36, 95% CI: 1.03-1.81).

— The Shores study evaluated a population of male veterans with low testosterone and found a decreased risk of all-cause mortality with TRT vs. no TRT (HR = 0.61, 95% CI: 0.42-0.88).

— The Muraleedharan study evaluated men with type 2 diabetes in the United Kingdom and found an increased risk of all-cause mortality in men with no TRT vs. those on TRT (HR = 2.30, 95% CI: 1.30-3.90).

— The Baillargeon study evaluated men enrolled in Medicare and found no overall increase in risk of hospitalization for MI in TRT users vs. non-TRT users (HR = 0.84, 95% CI: 0.69-1.02).

• A meta-analysis of 27 studies representing 2,994 patients demonstrated that TRT was associated with an increased risk of adverse CV events (odds ratio = 1.5, 95% CI: 1.1-2.1). Another meta-analysis of 26 studies representing 3,236 patients did not demonstrate a statistically significant increased risk of CV events associated with TRT.

— Both meta-analyses had methodological issues that limit conclusions.

• An FDA Advisory Committee recently convened to discuss the available data and concluded that the signal of CV risk associated with TRT is weak.

— Manufacturers are being required to conduct a clinical trial to more clearly address the question of whether an increased risk of MI or stroke exists with TRT use.

• A prior Clinical News Summary discussing TRT use and CV risk can be found here.