



**Indian Health Service  
National Pharmacy and Therapeutics Committee  
Formulary Brief: Testosterone Replacement  
-May 2015-**



**Background:** The IHS National Pharmacy and Therapeutics Committee reviewed testosterone products for men and women. Testosterone use has become popular in men, especially 40-64 year olds, for testosterone deficiency due to aging. A Food and Drug Administration (FDA) analysis of national sales data found that use of testosterone therapy rose 65% from 2009 to 2013 in the United States. The number of prescriptions rose from 1.3 million in 2010 to 2.3 million by 2013. Men aged 40 to 64 accounted for 70% of those prescribed testosterone products and were the group in whom usage increased the most during the 5-year period.

**Testosterone Therapy in Men:**

Declining testosterone levels and androgen deficiency is common. The Massachusetts Male Aging Study of 3,339 random men aged 40-79 years reported an annual decline of total testosterone of 0.8-1.6% and free testosterone of 1.7-2.8%. The Hypogonadism in Men Study of 2162 men >45 years old in primary care practices reported a prevalence of low testosterone levels of 38.7%. In 2010, The Endocrine Society Clinical Practice Guideline on Testosterone Therapy in Men with Androgen Deficiency Syndrome was published and provided recommendations for the evaluation and diagnosis of androgen deficiency. Despite the increasing number of prescriptions for testosterone products, data reveals that only half of men taking testosterone therapy had been diagnosed with androgen deficiency. In 25% of testosterone users, there is no evidence that testosterone concentrations were tested prior to initiating therapy and that 21% of those prescribed testosterone replacement had no testosterone levels tested at any time while on the therapy.

*Testosterone is available in the following delivery systems:*

Oral-tablet, buccal, sublingual	Parenteral	Subcutaneous implants	Transdermal-gels, patches	Nasal
methyltestosterone	testosterone cypionate	testosterone pellets	testosterone	testosterone
testosterone	testosterone enanthate			
testosterone undecanoate	testosterone propionate			
	testosterone undecanoate			

The potential benefits of testosterone replacement therapy include increase in bone density, improvement in body composition, strength, mood, and improvement in cognitive and sexual function. The potential adverse effects of testosterone therapy include increased risk of cardiovascular events, venous thromboembolism, erythrocytosis, lower urinary tract symptoms, obstructive sleep apnea, and prostate cancer.

On March 3, 2015, the FDA published a safety announcement stating that the benefit and safety of prescription testosterone products have not been established for the treatment of low testosterone levels due to aging. The FDA added the requirement that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications and the possibility of an increased risk for heart attacks and stroke. The announcement stated that health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests. This announcement was the result of a FDA advisory panel review of 5 observational studies and two meta-analyses. The five observational studies were retrospective cohort studies and showed conflicting results. Two studies found statistically significant increase in cardiovascular (CV) risk with testosterone therapy, two studies found a statistically significant mortality benefit with testosterone therapy, and one study was inconclusive. One meta-analysis

concluded an increased risk of CV events with testosterone and noted that industry supported studies were more likely to find testosterone therapy to not be associated with an increase in CV events. The other meta-analysis concluded that testosterone therapy correlated with a protective effect from CV events in men with metabolic derangements. Subsequent to the FDA's safety announcement, two studies presented at the American College of Cardiology Scientific Assembly and one study presented at The Endocrine Society meeting showed no increased risk of CV events in men receiving testosterone therapy.

### **Testosterone Therapy in Women:**

Androgens combined with estrogens have been used to treat menopause since 1940. It is estimated that in 1998, there were over 477 million postmenopausal women in the world. That number is projected to rise to 1.1 billion by the year 2025. In 1999, a study published in the Journal of the American Medical Association, "Sexual Dysfunction in the United States: Prevalence and Predictors," found that approximately 43% of postmenopausal women suffer from some form of female sexual dysfunction. The Endocrine Society released Clinical Guidelines for Androgen Therapy in Postmenopausal Women in 2014 which supported the use of testosterone therapy in postmenopausal women diagnosed with Hypoactive Sexual Desire Disorder according to DSM-V criteria. However, the testosterone delivery systems studied and recommended (transdermal patch/gel and vaginal gel) are not available in the United States. The American College of Obstetricians and Gynecologists clinical guidelines for vasomotor symptoms of menopause and vaginal atrophy published in January 2014, state that data does not support use of testosterone.

The FDA approved testosterone therapy for women to treat vasomotor symptoms related to menopause that are not relieved with estrogen alone is esterified estrogens combined with methyltestosterone. Women using testosterone therapy alone are obtaining the product from compounding pharmacies or using the formulations available for men. The benefits of testosterone therapy in women are improvement in sexual function and decreases in total cholesterol and triglycerides. Adverse effects are hirsutism and acne, decrease in HDL and increase in LDL. No change in body composition or bone mineral density has been demonstrated.

Further studies are needed to establish the safety and benefit of testosterone therapy in both men and women. There are currently no testosterone products on the NCF and no changes were made at the May meeting.

*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

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