**Drug Class Monograph**

**Class:** Testosterone Hormone Replacement  
**Drug:** Androderm (testosterone transdermal system), Androgel (testosterone topical gel), Axiron (testosterone topical solution), Aveed (testosterone undecanoate oil injectable), Fortesta (testosterone topical gel), Natesto (testosterone intranasal), Striant (testosterone buccal), Testim (testosterone topical gel), Testopel (testosterone pellets), Depo-Testosterone (testosterone cypionate injectable), Testosterone enanthate (testosterone injectable), Testosterone transdermal gel, Vogelxo (testosterone topical)  
**Line of Business:** Medi-Cal  
**Effective Date:** February 15, 2017  
**Revision Date:** February 15, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutic Subcommittee.

**Policy/Criteria:**

**Code-1 Criteria:**

1. **Testosterone Cypionate**  
   a. Restricted to the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

**Prior Authorization Criteria:**

1. **Treatment of hypogonadism**  
   a. Initial Authorization:  
      - Male;  
      - Documented pretreatment serum testosterone levels less than the laboratory’s lower reference limit;  
      - **Formulary Position:** Androderm, testosterone 1% transdermal gel and testosterone injectable (testosterone cypionate, testosterone enanthate) are the preferred agents.  

   b. Reauthorization:  
      - Serum testosterone level within or below normal limits of the reporting lab;  
      - OR Serum testosterone level outside of upper limits of normal for the reporting lab AND the dose is adjusted.
2. Treatment of HIV-associated male hypogonadism
   a. Initial Authorization:
      - Documented pretreatment total testosterone levels less than the median age-adjusted testosterone levels or less than the laboratory’s lower reference limit;
      - Prescribed by HIV or infectious disease specialist;
      - Formulary Position: Androderm, testosterone 1% transdermal gel and testosterone injectable (testosterone cypionate, testosterone enanthate) are the preferred agents.

   b. Reauthorization:
      - Documented clinical response (e.g. improvement in weight, lean body mass, testosterone level).

3. Treatment of HIV-associated wasting syndrome
   a. Initial Authorization:
      - Confirmed symptoms of muscle and/or weight loss (e.g. 10% or greater weight loss from baseline, or less than 90% ideal body weight);
      - Prescribed by Infectious Diseases/HIV specialist;
      - Formulary Position: Androderm, testosterone 1% transdermal gel and testosterone injectable (testosterone cypionate, testosterone enanthate) are the preferred agents.

   b. Reauthorization:
      - Documented clinical response (e.g. improvement in weight, lean body mass).

4. Treatment of advancing, metastatic (skeletal) mammary cancer in postmenopausal females
   a. Please refer to the Antineoplastic Drug Class Monograph.

5. Treatment of breast cancer in premenopausal females
   a. Please refer to the Antineoplastic Drug Class Monograph.

6. Requests for transgender hormonal treatment
   a. Please refer to Transgender Hormonal Treatment Pediatric Policy and Transgender Hormonal Treatment Adult Policy.
Clinical Justification:

2010 The Endocrine Society’s Clinical Guidelines: Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

- Recommend that clinicians measure morning total serum testosterone level by a reliable assay in patients with clinical manifestations or less specific symptoms and signs, as the initial diagnostic test.
- Recommend confirmation of the diagnosis by repeating measurement of total testosterone.
- Recommend measurement of free or bioavailable testosterone level, using an accurate and reliable assay, in some men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected.
- Recommend testosterone therapy for symptomatic men with confirmed classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being and bone mineral density.
- Recommend that clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass and muscle strength.
- The therapeutic target should be to raise serum testosterone levels into a range that is mid-normal for healthy, young men.

Summary

- Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone or a normal number of spermatozoa due to disruption of the hypothalamic-pituitary-testicular axis. Symptoms include reduced sexual desire and activity, fatigue, depression, lack of concentration, and sleep disturbances.
- Most T measurements in typical clinical laboratories may be >30% different from true serum T concentrations due to differences in assays and technique. The Endocrine Society recommends that clinicians use the lower reference limit for healthy young men established for the laboratory assay as the cut-off for hypogonadism. The American Urology Association suggests that when the results of the total testosterone are equivocal (230-350 ng/dL), it would be wise to confirm results with a second test measuring free testosterone levels.
- The target total testosterone range for young adult males on replacement therapy is 400-700 ng/dL. Most clinical studies on testosterone replacement were conducted in young males. Given that multiple comorbidities can lower total testosterone, such as age and obesity, some have suggested using age-adjusted testosterone levels to establish cut-offs and target levels for hypogonadism. However, no studies have validated using age-adjusted testosterone levels. The Endocrine Society suggests using a lower target range of 400-500 ng/dL in older adult males.
- The risks of testosterone replacement include the possibility of cardiovascular events, prostate growth, sleep apnea, urinary retention, and decreased HDL. It is not recommended to initiate therapy in patients with breast or prostate cancer.
- There is a high prevalence of low testosterone levels in HIV-infected men. Low testosterone levels in these patients result in weight and muscle loss, progression to
AIDS, and depression. The Infectious Diseases Society of America recommends obtaining morning testosterone levels in patients exhibiting fatigue, weight loss, or evidence of reduced bone mineral density and initiating short-term testosterone replacement once a diagnosis of hypogonadism is established. Obtaining free testosterone levels in this population may be useful to confirm diagnosis as many patients will have false normal testosterone levels due to elevated SHBG.

- Testosterone replacement is not recommended by the Infectious Diseases Society of America in eugonadal patients who present with HIV wasting syndrome. However, in one meta-analysis review of testosterone in HIV wasting syndrome, two small clinical studies that were included involved patients who were eugonadal at baseline. The conclusion of the meta-analysis was that testosterone was helpful for lean body mass recovery in patients with low to low-normal testosterone levels; however, safety with long-term testosterone administration remains unclear.

- According to the Endocrine Society’s Clinical Practice Guideline, Androgen Therapy in Women, although there is evidence for short-term efficacy of testosterone in selected populations such as surgically menopausal women, the generalized use of testosterone by women is not recommended, due to inadequate indication and evidence of safety in long-term studies.

References:

<table>
<thead>
<tr>
<th>Date</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/15/2017</td>
<td>• Testosterone cypionate added to code 1 for treatment of hypogonadism</td>
</tr>
</tbody>
</table>