Testosterone Injection and Implant

Description

Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone and Testone CIK (testosterone cypionate injection), Testopel (testosterone propionate implant)

Background

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics (1).

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include the following: impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis (1).

Androgens stimulate growth in adolescence and cause the eventual closure of the femoral epiphysis. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Chronic use may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been shown to stimulate the red blood cell production by the increased production of erythropoietic stimulating factor (2).

Regulatory Status

FDA-approved indications:
1. Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

2. Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

3. Delayed puberty in males: to induce pubertal changes in hypogonadal males.

4. In women as secondary treatment with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor (4).

Aveed carries a boxed warning which states that serious pulmonary oil microembolism (POME) reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. Because of the risk of this reaction and anaphylaxis, testosterone undecanoate is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Aveed REMS Program. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. The REMS program ensures the prescriber observes the patient in the health care setting for 30 minutes following each injection in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (3).

Chronic high dose therapy of androgens has shown development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma. Peliosis hepatitis can be a life-threatening or fatal complication. Low doses of 17-alpha-alkylandrogens have been associated with cholestatic hepatitis and jaundice. The medication should be discontinued and the cause should be determined if these conditions occur. Drug-induced jaundice is reversible upon withdrawal of medication therapy (3-6).
Male patients, with benign prostatic hyperplasia (BPH), must be monitored for worsening of signs and symptoms of BPH. Physicians should evaluate male patients for the presence of prostate cancer prior to the initiation of therapy. A normal prostate cancer risk is a PSA level that is less than 4 ng/ml. High prostate cancer risk patients, such as African American men and men whose father or brother had prostate cancer, should have a PSA less than 3 ng/ml. Check prostate-specific antigen (PSA) levels in men over age 50 years, or in those over age 40 having a family history of prostate cancer or if African-American; to ensure proper dosing. Patients should be re-evaluated 12 months after initiation of treatment, and then in accordance with prostate cancer screening practices (3-6).

Two total testosterone levels are required to determine medical necessity of testosterone replacement. Two morning samples, drawn between 8:00 a.m. and 10:00 a.m., obtained on different days are required. Total testosterone levels need to be below 300 ng/dL on both days in order to be considered for therapy (7).

Hematocrit levels must be less than 54% prior to initiation of testosterone therapy and reevaluated annually thereafter (3-6).

Androgen use for delayed puberty in males should be prescribed only by specialists who are aware of the adverse effects on bone maturation. An X-ray of the hand and wrist every 6 months will be required to determine bone age and to assess the effect of treatment on the epiphyseal centers (4).

Androgen therapy in the treatment for women with breast cancer should be made by an oncologist with expertise in this field. Hypercalcemia may occur in immobilized patients and in patients with breast cancer. If hypercalcemia occurs, the testosterone therapy should be discontinued (4).

Extreme caution should be used in patients with a history of cardiovascular disease (2).

Patients with severe obstructive sleep apnea and severe lower urinary tract symptoms are recommended not to use androgen therapy due to possible worsening of symptoms and/or even death (2).

**Related policies**
Testosterone topical, Testosterone oral / buccal / nasal, Testosterone powder
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone, Testone CIK (testosterone cypionate injection), and Testopel (testosterone propionate implant) may be considered **medically necessary** in male patients 18 years of age or older with deficiency of testosterone (hypogonadism); two morning testosterone levels that are less than 300ng/dL on different days; patients over 40 years of age must have baseline PSA less than 4 ng/ml and prostatectomy patients excluded from the requirement; absence of cancer and palpable prostate nodules; hematocrit level is less than 54%, and the patient will be monitored for worsening symptoms of benign prostatic hypertrophy (BPH) if there is a concurrent diagnosis and patient has had an evaluation of cardiovascular risk for MI, angina, stroke and there is absence of un-treated sleep apnea; no dual therapy with another testosterone product.

Delatextryl (testosterone enanthate injection), Depo-Testosterone, Testone CIK (testosterone cypionate injection), Testopel (testosterone propionate implant) may be considered **medically necessary** in **male** patients 12 years of age or older for treatment for delayed sexual development and/or puberty with confirmation of bone age of the hand and wrist (as determined by radiographic evidence), with liver function and hematocrit tests to be monitored every 6 months.

Delatestryl (testosterone enanthate injection) is considered **medically necessary** when used secondarily in **women** with previously treated inoperable metastatic breast or mammary cancer and confirmation that the following will be monitored every 6 months: hypercalcemia and agreement to discontinue the drug if present, liver function and hematocrit tests.

Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone, Testone CIK (testosterone cypionate injection), and Testopel (testosterone propionate implant) may be considered **investigational** for all other indications.

**Prior-Approval Requirements**

<table>
<thead>
<tr>
<th>Age</th>
<th>12 years of age or older</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
</tbody>
</table>

Patient must have the following:
Delay in sexual development and/or puberty

**AND** confirmation that the following will be monitored every 6 months:
1. Assess bone age of the hand and wrist (as determined by radiographic evidence)
2. Liver function tests
3. Hematocrit levels

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**Age**
18 years of age or older

**Gender**
Male

**Diagnosis**
Patient must have the following:
- Deficiency of testosterone (hypogonadism)

**AND ALL** of the following:
1. Two morning total testosterone levels less than 300 ng/dL on different days
2. Patients over 40 years of age must have baseline PSA less than 4 ng/ml
   a. Prostatectomy patients excluded from the requirement
3. Absence of current prostate cancer / palpable prostate nodules
4. Hematocrit less than 54%
5. If concurrent diagnosis of benign prostatic hypertrophy (BPH), then patient will be monitored for worsening symptoms
6. Evaluation of cardiovascular risk for MI, angina, stroke
7. Absence of un-treated sleep apnea
8. **NO** dual therapy with another testosterone product

**AND** the following for Aveed only:
- Physician has been certified by the Aveed REMS program

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**Age**
18 years of age or older

**Gender**
Female only

**Diagnosis**
Patient must have the following:
1. Inoperable metastatic breast or mammary cancer
2. The patient has received at least one prior therapy
AND confirmation that the following will be monitored every 6 months:
   a. Hypercalcemia and agreement to discontinue the drug if present
   b. Liver function tests
   c. Hematocrit level

**Prior – Approval ** Renewal Requirements

<table>
<thead>
<tr>
<th>Age</th>
<th>12 years of age or older</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male only</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Same as above</td>
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<table>
<thead>
<tr>
<th>Age</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Patient must have the following:
   Deficiency of testosterone (hypogonadism)

AND the following:
   1. Total testosterone levels of 800 ng/dL or less
   2. Absence of worsening effects of benign prostatic hypertrophy (BPH), if present
   3. Re-evaluation of cardiovascular risk for MI, angina, stroke
   4. NO dual therapy with another testosterone product

AND confirmation that the following will be monitored every 12 months:
   1. Serum testosterone concentrations
   2. Prostate specific antigen (PSA) for patients over 40 years of age
      a. Prostatectomy patients excluded from the requirement
   3. Hematocrit levels

<table>
<thead>
<tr>
<th>Age</th>
<th>18 years of age or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female only</td>
</tr>
<tr>
<td>Diagnosis</td>
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</table>
### Policy Guidelines

#### Pre - PA Allowance

None

#### Prior - Approval Limits

<table>
<thead>
<tr>
<th>Injectable Testosterone</th>
<th>Gender</th>
<th>Quantity</th>
<th>Days Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aveed (18 years of age or older)</td>
<td>Male</td>
<td>6ml</td>
<td>90</td>
</tr>
<tr>
<td>Delatestryl (testosterone enanthate)</td>
<td>Male</td>
<td>15ml</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>15ml</td>
<td>90</td>
</tr>
<tr>
<td>Depo-Testosterone (testosterone cypionate)</td>
<td>100mg/ml</td>
<td>Male</td>
<td>30ml</td>
</tr>
<tr>
<td></td>
<td>200mg/ml</td>
<td>Male</td>
<td>30ml</td>
</tr>
<tr>
<td>Testone CIK</td>
<td>200mg/ml</td>
<td>Male</td>
<td>3 kits</td>
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</table>

#### Implant Testosterone

<table>
<thead>
<tr>
<th>Implant Testosterone</th>
<th>Gender</th>
<th>Quantity</th>
<th>Days Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testopel Pellet</td>
<td>Male</td>
<td>6 pellets</td>
<td>90</td>
</tr>
</tbody>
</table>

**Duration** 6 months

#### Prior – Approval Renewal Limits

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<tbody>
<tr>
<td>Testopel Pellet (18 years of age or older)</td>
<td>Male</td>
<td>6 pellets</td>
<td>90</td>
</tr>
<tr>
<td>Testopel Pellet (12 – 17)</td>
<td>Male</td>
<td>6 pellets</td>
<td>90*</td>
</tr>
</tbody>
</table>

*One renewal
Duration 12 months

Rationale

Summary
Testosterone is approved for testosterone replacement therapy in men for conditions associated with a deficiency of testosterone such as: hypogonadotropic hypogonadism (congenital or acquired), primary hypogonadism (congenital or acquired), and delayed puberty. In women, testosterone therapy is approved to treat metastatic breast carcinoma.

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of the testosterone products Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone (testosterone cypionate injection), and Testopel (testosterone propionate implant) while maintaining optimal therapeutic outcomes.

References
Section: Prescription Drugs  Effective Date: October 1, 2015
Subsection: Endocrine and Metabolic Drugs  Original Policy Date: May 30, 2014
Subject: Testosterone Injection Implant  Page: 9 of 9

Date          Action
June 2014     Addition to PA
June 2014     Removal of absence of severe sleep apnea, severe lower urinary tract symptoms and addition of hematocrit level of 54%
               Revision of testosterone levels for continuation
August 2014   Revision of diagnosis for male patients 18 years or older to deficiency of testosterone/hypogonadism. Revision of renewal duration to 12 months.
October 2014  Revision on the Delatestryl and Depo-Testosterone injectable quantities to accommodate vial sizes. Change of age from 9 to 12 years of age for delayed puberty.
December 2014 Annual review and reference update. Change for patients over 40 years of age must have baseline PSA less than 4 ng/ml and prostatectomy patients excluded from the requirement
March 2015    Annual review and reference update.
April 2015    Addition of assessment of cardiovascular risk to criteria
June 2015     Addition of Testone CIK
               Addition of the evaluation of cardiovascular risk for MI, angina, stroke and absence of un-treated sleep apnea and no dual therapy with another testosterone product
September 2015 Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 18, 2015 and is effective October 1, 2015.

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