Clinical Policy Title: Implantable testosterone pellets

Clinical Policy Number: 18.03.05

Effective Date: June 1, 2018
Initial Review Date: April 10, 2018
Most Recent Review Date: May 1, 2018
Next Review Date: May 2019

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other healthcare providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of implantable hormone (testosterone) pellets to be clinically proven and, therefore, medically necessary as replacement therapy for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism, after courses of intramuscular or topical forms of testosterone have provided an inadequate response, are contraindicated, or the member is intolerant of these forms (FDA, 2015; CMS, 2015). Continuation of treatment using pellets will be necessary only if the patient’s testosterone level fails to increase to the normal range after six months of treatment (Bhasin, 2018).

In addition, AmeriHealth Caritas considers implantable testosterone pellets clinically proven and, therefore, medically necessary, as part of gender reassignment therapy for female-to-male individuals if courses of intramuscular or topical forms of testosterone have provided an inadequate response, are contraindicated, or the patient is intolerant of these forms (WPATH, 2011).

Limitations:
Testosterone therapy in hormone pellet or other forms for reduced levels of testosterone (confirmed by lab tests) due to aging is considered not clinically proven and, therefore, investigational/experimental (FDA, 2015).

Testosterone therapy in hormone pellet or other forms for patients with breast or prostate cancer or with a palpable prostate nodule or induration; with a prostate-specific antigen greater than 4 ng/mL or greater than 3 ng/mL in men at high risk for prostate cancer; with untreated severe obstructive sleep apnea; with severe lower urinary tract symptoms with International Prostate Symptom Score above 19; or with uncontrolled or poorly controlled heart failure is considered not clinically proven and, therefore, investigational/experimental (CMS, 2015; Bhasin, 2010).

Testosterone should not be prescribed as part of compounded hormones, such as in conjunction with estrogen, as these compounds are not approved by the U.S. Food and Drug Administration (FDA) and evidence for their effectiveness is lacking (ACOG, 2012; Santoro, 2016).

**Alternative covered services:**

None.

**Background**

Testosterone is a hormone generated by the testes essential for development and growth of male sex organs and maintenance of secondary male characteristics such as facial hair (FDA, 2015). Testosterone is present in women but at much lower levels than men. Levels of the hormone peak at about age 20 and starting in middle age decline by about 1 percent annually. The normal range of serum testosterone is 270 to 1,100 (average 679) nanograms per deciliter of blood (Davis, 2016).

Hypogonadism is a disorder marked by low levels of testosterone diagnosed through blood tests. In addition, the condition can occur from a variety of causes, including testicular problems, genetic problems, chemotherapy damage, or pituitary gland/hypothalamus disorders (FDA, 2015). Symptoms of hypogonadism can include reductions in libido, erections, physical energy, strength, stamina, and mental aggressiveness, along with weight gain, aches and pains, and osteoporosis (Davis, 2016).

A study by the Endocrine Society used a sample of 1,475 American males ages 30–79 to estimate that 5.6 percent have symptomatic low testosterone (<300 ng/dL), a figure that rises to 18.4 percent for males in their 70s. In addition, 24 percent and 11 percent had low total and free testosterone levels, respectively, regardless of whether symptoms were present. The Society projects that by 2025, there will be 6.5 million American males with symptomatic androgen deficiency, a rise of 38 percent from 2000 (Araujo, 2007).
The number of American males taking testosterone is rising rapidly. One study of 10,739,815 U.S. men over age 40 documented that from 2001 to 2011, use of testosterone (androgen) more than tripled, from 0.81 to 2.91 percent. Rates were greater for males in their 60s (3.75 percent, compared to 2.29 percent for males in their 40s), and in the South (3.77 percent in 2010, compared to the West [2.61 percent]), the Midwest (1.78 percent), and the Northeast (1.60 percent). A substantial proportion (25.28 percent) of users did not have their testosterone measured in the past 12 months. Common diagnoses in the year prior to treatment initiation were hypogonadism (50.58 percent), fatigue (34.49 percent), erectile dysfunction (31.88 percent), and psychosexual dysfunction (11.75 percent). Topical gel was the most commonly used treatment mode, and also rose more than any type, i.e., fivefold from 2001 to 2011 (Baillargeon, 2013).

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. The FDA endorses testosterone as replacement therapy only for men with hypogonadism due to disorders of the testicles, pituitary gland, or brain. These conditions include failure of the testicles to produce testosterone due to genetic problems, or damage from chemotherapy or infection. The FDA cautions that the benefits and safety of administering testosterone to symptomatic males with low levels of the hormone for no apparent reason other than aging have not been clinically proven (FDA, 2015).

The FDA also warns that possible increased risk of cardiovascular conditions, including heart attack, stroke, and death, have been identified in some peer-reviewed studies, while others found no such risks. The FDA encourages health providers to make patients aware of this potential risk when deciding to start or continue testosterone treatment, and requires manufacturers to conduct trials addressing this issue. Patients using testosterone should seek medical attention immediately if heart attack or stroke symptoms (chest pain, shortness of breath or difficulty breathing, weakness in one part/side of the body, or slurred speech) are present (FDA, 2015).

Testosterone pellets measure 3 mm x 9 mm and contain crystalline testosterone. Implantation is a brief procedure performed in an office setting. After cleaning the skin of the upper hip or buttocks, an anesthetic is injected and a small incision made. Typically, about 10–12 pellets are placed under the skin near the hip with a trocar. Testosterone is gradually released over 3–6 months (Case-Lo, 2017).

Testopel® (Slate Pharmaceuticals) became the first FDA-approved implantable testosterone pellet marketed in the United States in 2008. Pellets, as opposed to gels, eliminate the need for daily applications, erratic absorption, low long-term compliance rates, risk of transferring the gel to family members, and expense of the monthly prescriptions. Each pellet contains 75 mg of testosterone (McCullough, 2014).

The FDA guideline endorses implantable pellets of testosterone as replacement therapy for men who have hypogonadism from disorders of the testicles, pituitary gland, or brain. Pellets should only be used after courses of intramuscular and topical forms of testosterone have failed (FDA, 2015).
Other testosterone-related guidelines do not specifically address pellets. The Endocrine Society guideline recommends testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density (Bhasin, 2010). A March 2018 update of the Endocrine Society guideline addresses diagnostic techniques, criteria indicating treatment is needed, and monitoring. It also states the goal for success with any testosterone therapy is to achieve testosterone concentrations in the mid-normal range during treatments (Bhasin, 2018). This goal is based on results of the Testosterone Trial sponsored by the National Institutes of Health, in which 91 percent of 709 males over age 65 given testosterone increased and remained in the mid-normal range 3–12 months after treatment began (Snyder, 2016).

The Canadian Men’s Health Foundation Multidisciplinary Guidelines Task Force on Testosterone Deficiency recommends the same criteria as the FDA for treating males with low testosterone, without specifying pellets (Morales, 2015).

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on February 16, 2018. Search terms were: “testosterone,” “pellets,” “hypogonadism,” and “implant.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Health status in males taking testosterone have been tracked in numerous reports. A study of 1,167 Danish males ages 30–60 was followed a median of 15.2 years after testosterone levels were recorded. During follow-up, 36.1 percent (n=421) died. Men with the largest (below 10th percentile) in total testosterone had a significantly higher mortality risk (hazard ratio 1.60) than all others (Holmboe, 2018).
Some concern has been raised about testosterone therapy increasing the risk of cardiovascular morbidity. However, a recent literature review contends that only a few studies raised these concerns, and these were marred by serious methodological and analytical flaws; the article called the concerns “unsubstantiated” and that numerous trials and meta-analyses showed no such risk (Traish, 2016).

A systematic review of 75 studies (n=5,464) supported the conclusion of no causal association between testosterone therapy and cardiovascular disease (Corona, 2014). Another review (n=509) tracked males (average age 54 years) taking or not taking testosterone for 10 years, probably the first long-term study of testosterone risk. The review found an insignificant difference (4.4 percent versus 3.2 percent) in all-cause mortality between the two groups, and concluded that long-term therapy was safe (Eisenberg, 2015).

A systematic review of 45 trials (n=5,328) followed men with hypogonadism using testosterone for an average of 10.6 months. Testosterone supplementation was not linked with increased cardiovascular disease risk (p = 0.45). The rate of cardiovascular events was not significantly elevated for intramuscular testosterone (p = 0.91) or oral testosterone (p = 0.22), but was significantly greater for transdermal testosterone (p = 0.004) (Albert, 2016). A meta-analysis of 30 randomized trials showed no significant increase in risk of myocardial infarction, stroke, or mortality from testosterone use (Alexander, 2017).

A large systematic review and meta-analysis (87 randomized controlled trials and 51 nonrandomized studies) included studies of males over age 18 with low free and/or total testosterone tracked for at least three months. Significant increases in testosterone levels, along significant improvement in quality of life, libido, depression, and erectile dysfunction were identified (Elliott, 2017).

One early review of 380 men with hypogonadism undergoing 702 insertions of Testopel found that 6–10 or more pellets (450–750 or more mg) boosted total testosterone levels into normal range (over 300 nanograms per deciliter) after one month, and sustained normal levels for 4–6 months. Optimal and well tolerated results were eventually noted to be eight or more pellets (McCullough, 2012). Another dosing study from the same year concluded 10 – 12 pellets yielded optimal results (Pastuszak, 2012).

An early safety study of the safety of Testopel pellets included 80 men with 292 implant procedures. Compared to historical data of the Organon testosterone pellet, Testopel had a lower infection rate (0.3 percent versus 1.4–6.8 percent), and a lower pellet extrusion rate (0.3 percent versus 8.5–12.0 percent). No infections or pellet extrusions were reported and patient satisfaction was high (Cavender, 2009).

Outcomes comparing implantable testosterone pellets with injections, oral administration, and topical (gels) have been conducted. A systematic review of 59 studies (n=5,078), documented that, compared to placebo, parenteral and transdermal approaches were significantly more effective at increasing testosterone (mean differences 7.69 and 7.57) than were oral preparations (2.39) (Corona, 2016).

A systematic review of 16 randomized controlled trials (n=1,921) included those where subjects were followed for six months (seven trials) or 12 months (nine trials). Overall, testosterone lowered Aging
Male Symptoms \((p=0.0002)\), including higher lean body mass \((p=0.007)\), lower fat mass \((p=0.06, \text{ borderline significant})\), and lower total cholesterol \((p=0.01)\). Nonsignificant changes included body weight, body mass index, bone mineral density, and prostate-specific antigen. Average reductions in Aging Male Symptoms with transdermal methods (short-term) was significant at \(p=0.0001\), but not significant for injections at \(p=0.69\).

The study also documented insignificant differences between transdermal, oral, and injection modes of therapy for body weight \((p=0.23, 0.38, 0.55)\), body mass index \((p=0.86, 0.85, 0.91)\), and bone mineral density \((p=0.26, 0.60, 0.17)\). Patients in the transdermal group had significantly higher prostate-specific antigen \((p=0.0002 \text{ versus } 0.81 \text{ and } 0.27)\) and had significantly higher rates of adverse events (Guo, 2016).

In a systematic review of 15 studies \((n=739)\), average prostate-specific antigen was compared by type of testosterone treatment. In four studies, the difference in mean prostate-specific antigen levels were similar between patients who received transdermal testosterone and controls \((p<0.116)\), but significantly worse for those given intramuscular testosterone \((p<0.001)\). In two studies, the difference in change in levels were similar for both transdermal and intramuscular approaches \((p<0.875, p<0.787)\) (Kang, 2015).

A systematic review of 22 randomized controlled trials \((n=2,351)\), split into 11 short-term (<12 months) and 11 long-term (12–36 months) studies, compared prostate-related outcomes for testosterone therapy with placebo. Odds ratios for transdermal, oral, or injection administration of testosterone short-term were insignificantly low for prostate cancer \((1.10, 0.0, \text{ and } 0.39)\) and prostate nodules \((1.01, 0.0, \text{ and } 0.0)\). Long-term odds ratios were generally higher, with no difference from placebo \((3.06, 0.19, \text{ and } 2.09 \text{ for prostate cancer, and } 1.00, 0.97, \text{ and } 3.13 \text{ for prostate nodules})\) (Cui, 2015).

A study compared men with hypogonadism treated with gels \((n=47)\), injections \((n=57)\), or pellets \((n=74)\), followed for three years. Increases in total and free testosterone were observed for all groups, as they were for estradiol. The injection group had the highest increase, due to the much sharper rise in the first three months after therapy was initiated. Hemoglobin and hematocrit were higher in the injection group than in gel or pellet groups. No significant increases in prostate-specific antigen levels were observed. Erythrocytosis \((\text{hematocrit over } 50 \text{ percent})\) was more common with injections \((66.7 \text{ percent})\) than with gels \((12.8 \text{ percent})\) or pellets \((35.1 \text{ percent}, p < 0.0001)\) (Pastuszak, 2015).

Patient satisfaction among 382 patients using testosterone were similar across type of treatment \((\text{gels } 68 \text{ percent}, \text{ injections } 73 \text{ percent}, \text{ and implantable pellets } 70 \text{ percent})\) (Kovac, 2014).

**Policy updates:**

None.

**Summary of clinical evidence:**
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Albert (2016)</td>
<td><strong>Key points:</strong></td>
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</table>
| Risk of cardiovascular disease from testosterone | - Systematic review of 45 trials (n=5,328), men with hypogonadism on testosterone.  
- Subjects followed for an average of 10.6 months.  
- Testosterone supplementation not linked to cardiovascular disease risk (p = 0.45).  
- Cardiovascular event rate not significantly elevated for intramuscular (p = 0.91) or oral (p = 0.22), but significantly greater for transdermal testosterone (p=0.0004). |
| Corona (2016) | **Key points:**                   |
| Effectiveness of various types of testosterone in raising testosterone levels | - Systematic review of 59 studies (n=5,078), comparing types of testosterone therapy ability to increase testosterone levels.  
- Compared to placebo, parenteral and transdermal approaches were significantly more effective (mean differences 7.69 and 7.57) than oral preparations (2.39). |
| Guo (2016)    | **Key points:**                   |
| Changes in aging male symptoms from testosterone | - Systematic review of 16 randomized controlled trials (n=1,921); subjects followed for 12 months.  
- All testosterone lowered Aging Male Symptoms (p=0.0002).  
- Significant decreases in higher lean body mass (p=0.007), lower fat mass (p=0.06, borderline significant), and lower total cholesterol (p=0.01).  
- Nonsignificant changes included body weight, body mass index, bone mineral density, and prostate-specific antigen.  
- Average reductions in Aging Male Symptoms with transdermal methods (short-term) was significant at p=0.0001, but not significant for injections (long-term) at p=0.69.  
- Insignificant differences between transdermal, oral, and injection modes of therapy for body weight (p=0.23, 0.38, 0.55), body mass index (p=0.86, 0.85, 0.91), and bone mineral density (p=0.26, 0.60, 0.17).  
- Transdermal administration had significantly higher increased prostate-specific antigen (p=0.0002 versus 0.81 and 0.27) and had significantly higher rates of adverse events. |
| Cui (2015)    | **Key points:**                   |
| Risk of prostate disease from testosterone | - Systematic review of 22 randomized controlled trials (n=2,351) included 11 short-term (<12 months) and 11 long-term (12–36 months) studies.  
- Prostate-related outcomes for types of testosterone therapy compared with placebo.  
- Odds ratios for transdermal, oral, or injection administration of testosterone short-term were insignificantly low for prostate cancer (1.10, 0.0, and 0.39).  
- Odds ratios for transdermal, oral, or injection administration of testosterone short-term were insignificantly lower for prostate nodules (1.01, 0.0, and 0.0).  
- Odds ratios long-term for prostate cancer were 3.06, 0.19, and 2.09.  
- Odds ratios long-term for prostate nodules were 1.00, 0.97, and 3.13. |
### Citation

**Pastuszak (2015)**

Changes in levels of other hormones in males taking testosterone

### Content, Methods, Recommendations

**Key points:**

- Study of changes in serum hormones, erythrocytosis, lipids, and prostate-specific antigen for men with hypogonadism treated with gels (n=47), injections (n=57), or pellets (n=74).
- Subjects were followed for three years.
- Rises in total and free testosterone and in estradiol were observed for all groups.
- The injection group had the highest increase due to the much sharper rise in the first three months after therapy was initiated.
- Hemoglobin and hematocrit were higher for injections than gel or pellet groups.
- No significant increases in prostate-specific antigen levels were observed.
- Erythrocytosis (hematocrit over 50%) more common with injections (66.7%) than gels (12.8%) or pellets (35.1%, p<0.0001).

### References

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**
L33412. Testosterone pellets (Testopel®). Effective date October 1, 2015.
erageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=testosterone&KeyWordL
ookUp=Title&KeyWordSearchType=And&bc=gAAAAACAAAAA&. Accessed February 19, 2018.

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erageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=testosterone&KeyWordL
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**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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