

Corporate Medical Policy

Testosterone Pellet Implantation for Androgen Deficiency

File Name: testosterone_pellet_implantation_for_androgen_deficiency
Origination: 10/2015
Last CAP Review: 11/2018
Next CAP Review: 11/2019
Last Review: 11/2018

Description of Procedure or Service

Testosterone is produced primarily by the testes in response to stimuli from the hypothalamic and pituitary glands. Low testosterone is caused by deficient production of the hormone and is also known as androgen deficiency. Primary androgen deficiency results from failure of testosterone production at the testicular level in the presence of normal hypothalamic and pituitary function. Secondary androgen deficiency results from failure of production of androgen-stimulating hormones (luteinizing hormone, follicle-stimulating hormone) by the pituitary gland. It can be caused by dysfunction at the hypothalamic or pituitary level.

Hypogonadism is the clinical syndrome associated with androgen deficiency. The signs and symptoms of hypogonadism depend on the age of onset. In prepubertal individuals, the hallmark of androgen deficiency is the failure to develop secondary sex characteristics. In adults, the signs and symptoms are nonspecific, with the most specific symptoms related to sexual functioning such as decreased libido and erectile dysfunction. Symptoms are dependent on age, severity of androgen deficiency, duration of androgen deficiency, individual sensitivity to androgen, and comorbid illness. Symptoms and signs other than sexual dysfunction include loss of body hair, hot flushes or sweats, decreased energy, depression, sleep disturbance, reduced muscle mass and strength, and/or increased body fat. These can all occur in the absence of androgen deficiency and, therefore the diagnosis of hypogonadism can be challenging. A 2014 systematic review of studies that reported on risk factors, comorbidities, and consequences of male hypogonadism identified multiple comorbid conditions that were consistently risk factors for hypogonadism, including advanced age, obesity, a diagnosis of metabolic syndrome, and poor general health status. Multiple other conditions, including diabetes, coronary heart disease, hypertension, stroke, and peripheral artery disease were correlated with the presence of hypogonadism, although were not identified as risk factors.

Testosterone levels decrease with age beginning in the fourth or fifth decade, and this decrease is sometimes referred to as “andropause.” In the European Male Aging Study of 3220 men, there was a decline in serum testosterone levels of 0.4% per year between the ages of 40 and 70. Since this decline is gradual and modest, the clinical impact is uncertain. While there are also parallel decreases in androgen-dependent factors with age, such as sexual function, lean body mass, and bone mineral density, the degree to which these changes are due to decreasing testosterone has not been determined with certainty.

Because of the decline in testosterone levels with age, more elderly individuals will have low levels compared with younger individuals. Using a cutoff of 325 ng/dL as the lower limit of normal testosterone levels, 1 prospective cohort study of 890 men estimated that the rate of low testosterone is 20% for men in their 60s; 30% for men in their 70s; and 50% for men in their 80s. In this study, there were other factors that were associated with decreased testosterone, such as obesity and severe emotional stress. A much lower percentage of men have a combination of low testosterone levels and definite symptoms of hypogonadism. In the European Male Aging Study, this was estimated to be

Testosterone Pellet Implantation for Androgen Deficiency

present in 2.3% of men when using a cutoff of at least 3 symptoms potentially related to androgen deficiency.

Another factor that makes the diagnosis of hypogonadism challenging is the measurement of testosterone levels. Testosterone levels fluctuate substantially due to a variety of factors. There is a diurnal variation, which is more pronounced in younger individuals, with peak levels occurring in the early morning. This makes the timing of measurement important and requires repeated measurement before making a determination that testosterone is consistently low. Also, there is a wide range of levels seen in healthy individuals, and assigning the proper age-appropriate cutoff is controversial. Some individuals exhibit clear symptoms of hypogonadism with testosterone levels that are in the low normal range, while others with low levels do not experience any symptoms.

There are numerous different Food and Drug Administration (FDA)–approved formulations of testosterone that are available for replacement therapy. For most delivery preparations, FDA approval was granted on the ability to increase levels to the normal range and not on demonstration of beneficial clinical outcomes. This policy addresses subcutaneous pellet implantation of testosterone.

A depot formulation of testosterone is a subcutaneous testosterone tablet. These are placed subcutaneously in the buttocks, abdominal wall, or thigh under local anesthesia. They are replaced every 3 to 6 months. Limitations include the need for a minor surgical procedure, and local reactions at the implantation site, such as infections or fibrosis.

Regulatory Status

There are numerous preparations of testosterone that have received FDA approval for use in testosterone replacement therapy. These include intramuscular, oral, topical, subcutaneous and buccal preparations.

In March 2015, FDA issued a drug safety communication for prescription testosterone products. The communication stated: “We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.”

The communication also stated: “FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.”

NOTE: This policy does not apply to those undergoing treatments for gender confirmation.

Related Policy

Hormone Pellet Implantation for Hormone Replacement Therapy

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Testosterone pellet implantation may be considered medically necessary for the treatment of androgen deficiency when the criteria noted below are met.

Testosterone Pellet Implantation for Androgen Deficiency

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When testosterone pellet implantation for androgen deficiency is covered

Testosterone pellet implantation may be considered medically necessary under the following conditions:

- An established diagnosis of hypogonadism with androgen deficiency (see Policy Guidelines section) that includes:
 - Persistently low testosterone levels (at least 2 early morning serum total testosterone levels that are below the testing laboratory's lower limit of the normal range), AND
 - Multiple symptoms of hypogonadism including at least one "more specific" symptom (see Policy Guidelines section)
- HIV-infected individuals with low testosterone levels and weight loss; OR
- Individuals on chronic steroid treatment with low testosterone levels (see Policy Guidelines section).

When testosterone pellet implantation for androgen deficiency is not covered

Testosterone pellet implantation is considered investigational in all other situations in which the above criteria are not met, including but not limited to older individuals with low testosterone levels in the absence of clinical signs and symptoms of hypogonadism.

Policy Guidelines

Diagnosis and Monitoring of Androgen Deficiency

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of an individual who presents with symptoms of hypogonadism. Clinical Practice Guidelines recommend measuring serum testosterone only in individuals with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low normal range and alterations of serum hormone-binding globulin are suspected. Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is identified, the underlying etiology should be identified, and any reversible causes treated appropriately before consideration of testosterone replacement.

Individuals on chronic steroid treatment would be receiving ongoing treatment for manifestations of a chronic condition, as opposed to episodic treatment for an acute condition or acute flare of a chronic condition. The length of acute episodic steroid treatment may vary from several days to several months, but in most cases will be less than 4 to 6 weeks.

Persistently low testosterone levels refers to serum levels that are below the lower limit of normal on at least 2 occasions when measured in the early morning (approximately 8 am). The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society recommends that a lower limit for normal levels is 300ng/dL for total testosterone and 9.0 ng/dL for free testosterone. Joint guidelines by several

Testosterone Pellet Implantation for Androgen Deficiency

European and American specialty societies recommend that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL.

“More specific” symptoms of hypogonadism, as classified by the Endocrine Society, include the following:

- Incomplete or delayed sexual development
- Decreased libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of axillar and/or pubic body hair
- Very small (<5 mL) or shrinking testes
- Infertility due to low sperm count
- Height loss due to vertebral fractures, low trauma fractures, low bone density
- Hot flushes, sweats

The recommended dosing range for Testopel® (subcutaneous testosterone pellet) is 150 to 450 mg every 3 to 6 months. For 75-mg pellets, this would correspond to implant of 2 to 6 pellets every 3 to 6 months. The dosing interval is individualized, as some patients will require redosing as early as every 3 months while others may not require redosing for up to 6 months.

Monitoring of testosterone replacement should be performed beginning 3 to 6 months after replacement is initiated to ascertain whether serum levels are restored to the normal range, to determine whether clinical symptoms have improved, and to monitor for adverse effects. The goal of testosterone replacement is to raise levels into the mid-normal range. Higher replacement levels are unlikely to improve symptoms further and may increase the incidence and/or severity of adverse events.

Summary

For individuals who have androgen deficiency and clinical symptoms of hypogonadism who receive testosterone replacement therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and quality of life. For individuals with low testosterone levels and sexual dysfunction, the evidence is fairly consistent in demonstrating a beneficial effect on increased libido. Other sexual function symptoms such as erectile dysfunction are also likely to be improved, but the evidence is less strong. For nonsexual symptoms, there is evidence that lean body mass is increased, body fat is decreased, and bone mineral density is increased with testosterone therapy. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life and cognition, the evidence is limited and not consistent in reporting benefits of replacement therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have androgen deficiency and HIV infection who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials include patients with HIV infection and weight loss. These trials report improvements in body weight, lean body mass, and a decrease in body fat, which indicates that testosterone replacement is likely to ameliorate the weight loss associated with HIV infection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have androgen deficiency on chronic steroid treatment who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials include patients with androgen deficiency on chronic steroid treatment. These trials report improvements in body weight, lean body mass, and a decrease in body fat, which are likely to ameliorate the effects of chronic steroids on these parameters. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have androgen deficiency and type 2 diabetes who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and quality of life. The available RCTs report that

Testosterone Pellet Implantation for Androgen Deficiency

testosterone replacement leads to modest improvements in glucose control (e.g., hemoglobin A1c, insulin sensitivity). There is a lack of trials that report on clinical outcomes, and the small benefits may be outweighed by the adverse effects of treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For older individuals with low testosterone levels without definite hypogonadism who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and quality of life. The available RCTs are mostly small and report on a limited range of clinical outcomes. For most outcomes reported, there was no benefit reported for testosterone replacement. Some studies reported improvements in lean body mass and decreased body fat, and a recent RCT found improved sexual function. However, these studies do not report improvements in functional status or muscle strength. The evidence is insufficient to determine the effects of the technology on health outcomes.

The adverse event profile of testosterone therapy is not well-defined, but there are concerns for increased adverse prostate-related outcomes and cardiovascular outcomes. This uncertainty in the adverse event profile creates challenges in determining the risk/benefit profile of treatment in otherwise healthy individuals.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 11980, S0189

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab*. Jul 2008;93(7):2737-2745. Retrieved at http://www.researchgate.net/publication/5582341_Hypothalamic-Pituitary-Testicular_Axis_Disruptions_in_Older_Men_Are_Differentially_Linked_to_Age_and_Modifiable_Risk_Factors_The_European_Male_Aging_Study on September 16, 2015.

Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. Drug Safety Communications 2014; <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM383909.pdf> . Accessed September, 2015.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010 Jun;95(6):2536-59. <http://press.endocrine.org/doi/full/10.1210/jc.2009-2354>

Zarotsky V, Huang MY, Carman W, et al. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology*. Nov 2014;2(6):819-834.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.23, 12/11/2014

Testosterone Pellet Implantation for Androgen Deficiency

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.23, 12/10/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.23, 10/13/2016

For Policy titled Testosterone Pellet Implantation for Androgen Deficiency

Specialty Matched Consultant Advisory Panel 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.23, 7/13/2017

Specialty Matched Consultant Advisory Panel 11/2017

Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* May 1 2018;103(5):1715-1744. PMID 29562364. Retrieved at <https://academic.oup.com/jcem/article/103/5/1715/4939465> on September 25 2018.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.23, 7/12/2018

Specialty Matched Consultant Advisory Panel 11/2018

Policy Implementation/Update Information

10/30/15 New policy developed. Testosterone replacement therapy is medically necessary for men with androgen deficiency and symptoms of hypogonadism; for HIV patients with low testosterone levels and weight loss; and for patients on chronic steroid treatment with low testosterone levels. Testosterone replacement therapy is investigational in all other situations. Notification given 10/30/15 for effective date 12/30/15. (sk)

2/29/16 Reference added. Policy Guidelines updated. (sk)

For Policy titled Testosterone Pellet Implantation for Androgen Deficiency

1/27/17 Reference added. Specialty Matched Consultant Advisory Panel review 11/30/16. Title changed from Testosterone Pellet Implantation for Androgen Deficiency in Men to Testosterone Pellet Implantation for Androgen Deficiency. (sk)

8/11/17 Reference added. (sk)

12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. (sk)

10/12/18 References added. (sk)

12/14/18 Specialty Matched Consultant Advisory Panel review 11/28/2018. No change to policy intent. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.