Implantable Hormone Pellets

Policy # 00073
Original Effective Date: 01/26/2004
Current Effective Date: 06/20/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider implantable testosterone pellets for use in males for the treatment of primary or secondary hypogonadism OR delayed puberty to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility will be considered for implantable testosterone pellets when the following criteria are met:

- An established diagnosis of hypogonadism with androgen deficiency (see Policy Guidelines section) that includes:
    - Persistently low testosterone levels; AND
    - Multiple symptoms of hypogonadism including at least 1 "more specific" symptom (see Policy Guidelines section); OR
- Hormone pellet implantation is being used for treatment of delayed male puberty.

Note: For treatment of delayed male puberty a six-month-or-shorter course of androgen may be indicated for induction of puberty in patients with familial delayed puberty, a condition characterized by spontaneous, nonpathologic, late-onset puberty.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of implantable hormone testosterone pellets when patient selection criteria are not met, including but not limited to older men with low testosterone levels in the absence of clinical signs and symptoms of hypogonadism, to be **investigational.***

Based on review of available data, the Company considers the use of implantable hormone testosterone pellets for non-U.S. Food and Drug Administration (FDA) approved indications to be **investigational.***

Based on review of available data, the Company considers the use of implantable hormone estradiol pellets to be **investigational.***

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Policy Guidelines

DIAGNOSIS OF ANDROGEN DEFICIENCY

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a man who presents with symptoms of hypogonadism. Clinical practice guidelines recommend measuring serum testosterone only in men 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 (Bhasin et al, 2010). 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.

Persistently low testosterone levels refers to serum levels below the lower limit of normal on at least 2 occasions when measured in the early morning (≈8:00 A.M.). The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society has recommended a lower limit for normal levels is 300 ng/dL for total testosterone and 9.0 ng/dL for free testosterone (Bhasin et al, 2010). Joint guidelines by several European and American specialty societies have recommended that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL (Wang et al, 2009).

"More specific" symptoms of hypogonadism, as classified by the Endocrine Society, include the following (Bhasin et al, 2010):

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

TESTOSTERONE DOSAGE GUIDELINES

Dosing of testosterone is variable, depending on age, baseline testosterone levels, comorbid disease, response to initial replacement levels, and adverse reactions. General dosing guidelines are provided by Endocrine Society. Specific dosing guidelines, taken from the product prescribing information:

- **Testopel®‡:** The recommended dosing range is 150 to 450 mg every 3 to 6 months. For 75-mg pellets, this would correspond to the implantation of 2 to 6 pellets every 3 to 6 months. The dosing interval is individualized because some patients will require redosing as early as every 3 months while others may not require redosing for up to 6 months.

MONITORING STRATEGIES FOR PATIENTS ON TESTOSTERONE THERAPY

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.

Recommendations for monitoring for testosterone-related adverse events have been provided by Endocrine Society guidelines on testosterone therapy in men with androgen deficiency (see Practice Guidelines and Position Statements section) (Bhasin et al, 2010). These recommendations include:

- Determine hematocrit levels at baseline, at 3 to 6 months, and then annually. If the hematocrit level is above 54%, stop therapy until the hematocrit level decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose.
- Repeating bone mineral density of the lumbar spine, femoral neck, and hip after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.
- In men 40 years of age or older who have a baseline prostate-specific antigen (PSA) concentration greater than 0.6 ng/mL, conduct a digital examination of the prostate and PSA measurement before initiating treatment, at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient.
- Obtain urologic consultation if there is:
    - An increase in serum or plasma PSA concentration greater than 1.4 ng/mL within any 12-month period of testosterone treatment.
    - A PSA velocity of more than 0.4 ng/mL per year using the PSA level after 6 months of testosterone administration as the reference. PSA velocity should be used only if there are longitudinal PSA data for more than 2 years.
    - Detection of a prostatic abnormality on digital rectal examination.
    - American Urological Association/International Prostate Symptom Score above 19.

Practice Guidelines and Position Statements

Endocrine Society

The Endocrine Society published clinical practice guidelines on testosterone therapy in men with androgen deficiency in 2006, with an update published in 2010. The 2010 guidelines included the following statements on the diagnosis of androgen deficiency and therapy with testosterone replacement:

- We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. (Strong recommendation; very low quality of evidence).
- We recommend testosterone therapy for symptomatic men with 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 (Strong recommendation; low quality of evidence).
- We recommend against testosterone therapy in patients with breast or prostate cancer. (Strong recommendation; quality of evidence very low for breast cancer, low for prostate cancer).
- We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy. (Strong recommendation; very low quality of evidence).

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An update to these guidelines was published in 2015. The following recommendations were amendments to the 2010 guidelines:

- "Men with metabolic syndrome, who were previously unexamined by the 2010 Endocrine Society Clinical Practice Guidelines, may benefit from testosterone replacement therapy (TRT) based on improvements in biometrics and insulin sensitivity. Effects of TRT on similar endpoints in men with type 2 diabetes mellitus remain unclear."
- "Effects of TRT on erectile function, even in men refractory to phosphodiesterase type 5 inhibitors, and on quality of life in men with erectile dysfunction remain inconclusive."
- "There is no new level 1 evidence to support a definitive connection between TRT and cardiovascular morbidity to support a change in recommendations."
- "There is no new level 1 evidence to support a connection between TRT in men with previously treated or active prostate cancer to support a change in recommendations."

Background/Overview

Hormone pellets contain either estrogen (estradiol) or testosterone and are implanted subcutaneously to provide hormone replacement therapy (HRT). The pellets provide a slow, continuous release of hormone into the bloodstream and, unlike oral hormone replacement, are not metabolized by the liver. The pellets can last up to six months, but are more typically replaced every three to four months. Frequently, this is the last resort being used after traditional methods of administration (oral, injection or dermal patch) have failed or been poorly tolerated due to side effects.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Numerous preparations of testosterone have been approved by FDA for use in TRT. They 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."

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Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Testosterone
Androgen deficiency, also known as hypogonadism, results from the sub-normal production of testosterone by the testes. Testicular failure may have a genetic or a developmental basis, or may be acquired. Hypogonadotropic (secondary) hypogonadism may result from either acquired or congenital defects in pituitary or hypothalamic function. The efficacy of long acting subcutaneous testosterone pellets as a form of maintenance treatment in hypogonadal males has been proven through randomized clinical trials.

The aging male population in the United States is expected to significantly increase between 2000 and 2030.The normal aging process in men is associated with a slow and irregular decline in blood testosterone levels. This testosterone deficiency produces symptoms similar to those associated with aging, such as loss of energy, depression, decreased libido, erectile dysfunction, loss of bone and muscle mass with decreased muscle strength, increased fat mass and frailty. Several randomized placebo-controlled studies of androgen therapy indicated that testosterone replacement can improve some of these symptoms. However, the studies have not assessed potential risks associated with testosterone replacement, in particular, cardiovascular or prostatic disease. TRT is not recommended in healthy older men due to the uncertainty of the benefit/risk ratio.

Estradiol
There were several randomized controlled trials evaluating the efficacy of estrogen pellet implants, along with a number of uncontrolled prospective clinical trials, case series reports and retrospective studies. In some studies, estrogen implant therapy was compared with placebo, while in others it was compared with oral or transdermal estrogen replacement therapy. Most of the studies identified for review involved relatively small numbers of subjects, especially considering the numbers of women who are potential candidates for HRT. Additionally, most of the studies did not involve any kind of blinding, and none were completely blinded. Moreover, the effect of estrogen implants on climacteric symptoms was determined largely with subjective and patient-reported measures. Therefore, these studies may be subject to bias due to a significant placebo effect. Evaluation of the ability of estrogen implants to reduce or prevent the development of osteoporosis involved objective measures of bone density, and was likely subject to fewer biases. Only three of the studies reported on the effect of estrogen implants on lipoprotein profiles, and none provided sufficient long term data to evaluate the impact of estrogen implant therapy on risk of future cardiac events. Duration of follow-up was generally one to three years, although a few studies provided data on patients who had received estrogen implant therapy for more than 10 years.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Testosterone Replacement Therapies”, 5.01.23, 7:2017.

2. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. Arch Dis Child. 1997 Jun; 76(6):495-9.
3. Liu PY, Swerdloff R. The Rationale, Efficacy and Safety of Androgen Therapy in Older Men: Future Research and Current Practice Recommendations. J Clin Endocrinol Metab. 2004 Oct; 89:4789-96.
4. Hijazi R, Cunningham G. Andropause: Is Androgen Replacement Therapy Indicated for the Aging Male? Annu Rev Med. 2004 Aug; 20:117-137.

Policy History

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11/18/2003	Medical Policy Committee review
01/26/2004	Managed Care Advisory Council approval
12/07/2004	Medical Director review
12/21/2004	Medical Policy Committee review. Format revision. No substance change to policy.
01/31/2005	Managed Care Advisory Council approval
02/01/2006	Medical Director review
02/15/2006	Medical Policy Committee review. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
02/23/2006	Quality Care Advisory Council approval
03/14/2007	Medical Director review
03/21/2007	Medical Policy Committee approval
03/12/2008	Medical Director review
03/19/2008	Medical Policy Committee approval. No change to coverage eligibility.
03/04/2009	Medical Director review
03/18/2009	Medical Policy Committee approval. No change to coverage.
12/04/2009	Medical Policy Committee approval.
12/16/2009	Medical Policy Implementation Committee approval. Deleted the When Services are not covered section. Added statement to deny investigational for off label use. Deleted the requirement of second line therapy.
06/03/2010	Medical Policy Committee Approval. Policy revised to add back statement concerning estradiol pellets coverage eligibility; non-covered.
06/16/2010	Medical Policy Implementation Committee approval
06/02/2011	Medical Policy Committee approval.
06/15/2011	Medical Policy Implementation Committee approval. No change to coverage.
06/14/2012	Medical Policy Committee review.
06/20/2012	Medical Policy Implementation Committee approval. No change to coverage.
06/06/2013	Medical Policy Committee review.
06/25/2013	Medical Policy Implementation Committee approval. No change to coverage.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review

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06/21/2017	Medical Policy Implementation Committee approval. Added policy guidelines and practice guidelines sections. Revised first coverage indication to include criteria.
10/01/2017	Coding update
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Added "including but not limited to older men with low testosterone levels in the absence of clinical signs and symptoms of hypogonadism" to the investigational statement for use of implantable hormone testosterone pellets when patient selection criteria are not met. Added sections from BCBSA Policy Guidelines for "Diagnosis Of Androgen Deficiency", "Testosterone Dosage Guidelines" and "Monitoring Strategies For Patients On Testosterone Therapy".

Next Scheduled Review Date: 06/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	11980			
HCPCS	J3490, S0189			
ICD-10 Diagnosis	E29.0	E29.8	E30.00	E34.0
	E34.50-E34.51	E89.5	N44.00	N45.1-N45.4
	E50.0	N51	N89.7	N91.0-N91.5
	N92.0-N92.6	N93.0-N93.9	N95.0-N95.9	N97.0
	Q53.00-Q53.02	Q53.10-Q53.13	Q53.20-Q53.23	Q53.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.