Subject:	Subcutaneous Hormonal Implants		
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Overview

This document addresses the use of Testopel (testosterone subcutaneous implant) along with other subcutaneous hormone implants.

Testosterone is an androgen hormone responsible for normal growth and development of male sex characteristics. In certain medical conditions such as hypogonadism, the endogenous level of testosterone falls below normal levels. Primary hypogonadism includes conditions such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, or vanishing testis syndrome; bilateral orchidectomy; and inborn errors in the biosynthesis of testosterone. Secondary hypogonadism, also called hypogonadotropic hypogonadism includes conditions such as gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury resulting from tumors, trauma, surgery, or radiation.

In 2015, the Endocrine Society added the following amended recommendations:

- 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 (Seftel, 2015).

The Endocrine Society published clinical practice guidelines on Testosterone Therapy in Men with Androgen Deficiency in 2006, with an update published in 2018 (Bhasin). The 2018 guidelines included the following statements for the diagnosis of androgen deficiency and therapy with testosterone replacement:

- We recommend making the diagnosis of hypogonadism in men with consistent symptoms and signs and unequivocally and consistently low serum testosterone levels. (Strong recommendation; moderate quality of evidence);
- We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency (Strong recommendation; moderate quality of evidence);
- We recommend against testosterone therapy in men planning fertility in the near term or men with breast or prostate cancer, a palpable prostate nodule or induration
- We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia (Strong recommendation; low quality of evidence).
- We suggest that clinicians assess prostate cancer risk in men being considered for testosterone therapy. (Conditional recommendation; very low quality of evidence);
- We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations (Strong recommendation; low quality of evidence).
- In men > 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (Conditional recommendation, very low quality of evidence);
- We suggest initiating testosterone therapy with any of the following regimens (75 to 100 mg of testosterone enanthate or cypionate administered IM weekly, or 150 to 200 mg administered every 2 weeks, injectable testosterone undecanoate; also

patches, gel, buccal tablets, implanted pellets) chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. (Weak recommendation; strength of evidence low).

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. 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 prior to consideration of testosterone replacement.

Persistently low testosterone levels refers to serum levels that are below the lower limit of normal on at least two occasions when measured in the early morning. The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society recommends that a lower limit for normal levels is 264 ng/dL* for total testosterone and 9.0 ng/dL for free testosterone… We suggest monitoring testosterone levels 3 to 6 months after initiation of testosterone therapy and then annually to assess whether symptoms have responded to treatment and whether the individual is suffering from any adverse effects. Therapy should aim to raise the serum testosterone level into the mid-normal range. For injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is > 700 ng/dl (24.5 nmol/liter) or < 400 ng/dl (14.1 nmol/liter), adjust dose or frequency. Testosterone pellets, measure testosterone levels at the end of dosing intervals. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range. (Bhasin, 2010)

**Lower limit of normal for total testosterone (TT) harmonized to the CDC standard in healthy nonobese young men; this limit could be used for TT assays that are CDC certified. For laboratories that are not CDC certified, reference range may vary considerably depending on assay and reference population used.*

The Endocrine Society also provided the following list of specific symptoms of hypogonadism:

- 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 (Bhasin, 2010).

Regarding hypogonadism associated with male aging, in 2009 the International Society for the Study of Aging Male, the International Society of Andrology, the European Association of Urology, the European Academy of Andrology, and the American Society of Andrology issued joint guidelines on the treatment and monitoring of late-onset hypogonadism which provided the following:

The diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency (Grade A recommendation; level of evidence 3). The symptom most associated with hypogonadism is low libido (Grade A recommendation; level of evidence 3). Other manifestations of hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency. One or more of these symptoms must be corroborated with a low serum testosterone level (Grade A recommendation; level of evidence 3).

Presentations of natural testosterone should be used for substitution therapy. Currently available intramuscular, subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective (Grade A recommendations; level of evidence 1b). The selection of the preparation should be a joint decision of an informed patient and physician (Wang, 2009).

While estrogen replacement can be beneficial in the treatment of menopausal symptoms, subcutaneous estrogen or estrogen containing preparations are non-FDA approved.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Testopel (subcutaneous testosterone implants)

Requests for Testopel (subcutaneous testosterone implants) **for hormone replacement therapy** may be approved if the following criteria are met:

I. Individual is male; **AND**
II. Individual is 18 years of age or older; **AND**
III. Documentation is provided that prior to starting testosterone therapy, an initial and a repeat (at least 24 hours apart) morning total testosterone level is provided to confirm a low testosterone serum level indicating one of the following:
    A. Individual is 70 years of age or younger with a serum testosterone level of less than 300 ng/dL; **OR**
    B. Individual is over 70 years of age with a serum testosterone level of less than 200 ng/dL; **AND**
IV. Individual has one of the following conditions:
    A. Primary hypogonadism (congenital or acquired) (for example, bilateral torsion, cryptorchidism, chemotherapy, Klinefelter Syndrome, orchitis, orchiectomy, toxic damage from alcohol or heavy metals, vanishing testis syndrome, idiopathic primary hypogonadism, age-related hypogonadism [also referred to as late-onset hypogonadism]); **OR**
    B. Hypogonadotropic hypogonadism (also called secondary hypogonadism) (congenital or acquired) (for example, idiopathic gonadotropic or luteinizing hormone-releasing hormone [LHRH] deficiency, pituitary-hypothalamic injury); **AND**
V. Individual presents with symptoms associated with hypogonadism, such as, but not limited to at least one of the following (A-through I):
    A. Reduced sexual desire (libido) and activity; **OR**
    B. Decreased spontaneous erections; **OR**
    C. Breast discomfort/gynecomastia; **OR**
    D. Loss of body (axillary and pubic) hair, reduced need for shaving; **OR**
    E. Very small (especially less than 5 mL) or shrinking testes; **OR**
    F. Inability to father children or low/zero sperm count; **OR**
    G. Height loss, low trauma fracture, low bone mineral density; **OR**
    H. Hot flushes, sweats; **OR**
    I. Other less specific signs and symptoms including decreased energy, depressed mood/dysthymia, irritability, sleep disturbance, poor concentration/memory, diminished physical or work performance.

Requests for Testopel (subcutaneous testosterone implants) **for continuation of hormone replacement therapy** may be approved if the following criteria are met:
I. Individual met all diagnostic criteria for initial therapy; **AND**
II. Documentation is provided that individual has had serum testosterone level measured in the previous 180 days and the value is below or within the therapeutic range based on laboratory reference range; **AND**
III. Individual has obtained clinical benefits as noted by symptom improvement.

Requests for Testopel (subcutaneous testosterone implants) **for delayed puberty** may be approved if the following criteria are met:
I. Individual is a male 14 years of age or older; **AND**
II. Individual is using hormone to stimulate puberty; **AND**
III. Documentation is provided indicating few to no signs of puberty.

Requests for Testopel (subcutaneous testosterone implants) **for transgender individuals** may be approved if the following criteria are met:

I. Individual is 16 years of age or older; **AND**
II. Individual has a diagnosis of gender dysphoria/incongruence or gender identity disorder; **AND**
III. The goal of treatment is female-to-male gender reassignment.

Requests for Testopel (subcutaneous testosterone implants) may not be approved for the following criteria:

I. Hormone replacement therapy (HRT) for female menopause; **OR**
II. Delayed puberty in females.

Requests for Testopel (subcutaneous testosterone implants) may not be approved when the above criteria are not met and for all other indications.

Estrogen and estrogen containing combination subcutaneous implanted agents

Requests for estrogen and estrogen containing combination subcutaneous implanted agents will not be approved. These agents are not FDA approved.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin) [when specified as implantation of testosterone pellets]

HCPCS

S0189	Testosterone pellet; 75mg
J3490	Unlisted drugs when specified as Estrogen and estrogen containing combination subcutaneous implanted agents

ICD-10 Diagnosis

E23.0	Hypopituitarism (hypogonadotropic hypogonadism)
E29.1	Testicular hypofunction
E29.8	Other testicular dysfunction
E29.9	Testicular dysfunction, unspecified
E30.0	Delayed puberty
E89.5	Postprocedural testicular hypofunction
F64.0-F64.9	Gender identity disorders
N44.00-N44.04	Torsion of testis
N45.2	Orchitis
N46.11-N46.129	Oligospermia
N52.01-N52.9	Male erectile dysfunction
Q53.00-Q53.9	Undescended and ectopic testicle
Q55.22	Retractile testis
Q98.0-Q98.1	Klinefelter syndrome (karyotype 47 XXY/male with more than two X chromosomes
Q98.4	Klinefelter syndrome, unspecified
R68.82	Decreased libido
T88.7XXA-T88.7XXS	Unspecified adverse effect of drug or medicament

Document History

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Document History:

- 08/19/2022– Annual Review: No changes. Coding reviewed: No changes.
- 09/13/2021– Annual Review: No changes Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 09/14/2020 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/16/2019 – Annual Review: Minor wording change to clarify reference range dependent on laboratory, and formatting changes. Coding reviewed: No changes.
- 06/10/2019 – Selected Review: Updated document name; added may not be approved criteria for estrogen and estrogen containing combination subcutaneous implanted agents.
- 11/09/2018 – Coding Review: no changes.
- 08/17/2018 – Annual Review: First review of DRUG.00031 – no recommended changes.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.