Implantable hormone pellets include the following:

- FDA approved Testopel® (testosterone pellets)
- Compounded testosterone pellets
- Compounded estrogen and estrogen derivative pellets (for example, estradiol, estriol, estrone)
- Compounded progesterone and progesterone derivative pellets (for example, progestin)

**Cigna covers Testopel® (testosterone pellets) as medically necessary in males when either of the following criteria is met:**

- Diagnosis of hypogonadism or hypogonadotropic hypogonadism (congenital or acquired) in an individual 18 years of age or older as confirmed by BOTH of the following:
  - Documentation of signs and symptoms of androgen deficiency
  - Two early morning, low total serum testosterone levels drawn on different days. Low serum testosterone level is defined as ANY of the following:
    - Below the laboratory’s normal reference range
    - Total testosterone level less than 280 ng/dL (9.7 nmol/L)
    - Free testosterone level less than 5 pg/ml (0.17 nmol/L)
- Diagnosis of delayed puberty in an individual 14 years of age or older as confirmed by BOTH of the following:
  - Documentation of limited or no signs of puberty
  - Testosterone is being used short term (4 to 6 months) to stimulate puberty

Initial approval quantity limit is 6 pellets per 90 days.
Quantities beyond 6 pellets per 90 days require:

- Documentation of continued signs and symptoms of androgen deficiency
- Documentation of a persistent early morning, low testosterone level. Low serum testosterone level is defined as ANY of the following:
  - Below the laboratory's normal reference range
  - Total testosterone level less than 280 ng/dL (9.7 nmol/L)
  - Free testosterone level less than 5 pg/ml (0.17 nmol/L)

Cigna does not cover Testopel (testosterone pellets) for any other indication including the following because it is considered experimental, investigational or unproven.

- Treatment of menopausal symptoms

Cigna does not cover compounded testosterone pellets for any indication because they are considered experimental, investigational or unproven.

Cigna does not cover implantable estrogen/estrogen derivative pellets (either estrogen/estrogen derivative alone or in combination with testosterone) or implantable progesterone/progestin pellets for treatment of menopausal symptoms or any other indication because they are considered experimental, investigational or unproven.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Testopel® (testosterone pellets).

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

**FDA Approved Indication**

(There are no FDA-approved, commercially available formulations of implantable estrogen or progesterone/progestin pellets.)

**MALES**

Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

- Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome; or orchiectomy.
- Hypogonadotrophic hypogonadism (congenital or acquired) - idiopathic or gonadotropic LHRH deficiency, or pituitary - hypothalamic injury from tumors, trauma or radiation.

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sex characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

The safety and efficacy of Testopel (testosterone pellets) in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.

Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be taken every 6 months to assess the effect of treatment on epiphyseal centers.

**FDA Recommended Dosing**
Prior to initiating Testopel (testosterone pellets), confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

The suggested dosage for androgens varies depending on the age, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions. The dosage guideline for the testosterone pellets for replacement therapy in androgen-deficient males is 150mg to 450mg subcutaneously every 3 to 6 months. Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower doses initially, gradually increasing the dose as puberty progresses, with or without a decrease in maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

Dosages in delayed puberty generally are in the lower range of that listed above and, for a limited duration, for example 4 to 6 months.

The number of pellets to be implanted depends upon the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. The usual dosage is as follows: implant two 75 mg pellets for each 25 mg testosterone propionate required weekly. Thus when a patient requires injections of 75 mg per week, it is usually necessary to implant 450 mg (6 pellets). With injections of 50 mg per week, implantation of 300 mg (4 pellets) may suffice for approximately three months. With lower requirements by injection, correspondingly lower amounts may be implanted. It has been found that approximately one-third of the material is absorbed in the first month, one-fourth in the second month and one-sixth in the third month. Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months.

**Drug Availability**

(There are no FDA-approved, commercially available formulations of implantable estrogen nor or progesterone/progestin pellets.)

Each testosterone pellet contains 75 mg testosterone, one individual pellet per vial. Testosterone pellets are classified as a Schedule III controlled substance under the Anabolic Steroids Act of 1990.

**General Background**

**Pharmacology**

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution such as beard, pubic, chest and axillary hair, laryngeal enlargements, vocal cord thickening, alterations in body musculature and fat distribution. Drugs in this class can also cause retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth which is brought about by the fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

**Clinical Efficacy**
Testopel received FDA approval in 1972 when labeling requirements were less stringent, and as such, there is no clinical efficacy information available in the current label.

FDA Warning
As of October 2016, the FDA approved class-wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other AAS.

The Anabolic Steroids Control Act of 1990 placed AAS, including testosterone, in Schedule III of the Controlled Substances Act. Testosterone and other AAS are abused by adults and adolescents, including athletes and body builders. Abuse of testosterone, usually at doses higher than those typically prescribed and usually in conjunction with other AAS, is associated with serious safety risks affecting the heart, brain, liver, mental health, and endocrine system. Reported serious adverse outcomes include heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms, such as depression, fatigue, irritability, loss of appetite, decreased libido, and insomnia.

The new Warning will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse. In addition to the new Warning, all testosterone labeling has been revised to include information in the Abuse and Dependence section about adverse outcomes reported in association with abuse and dependence of testosterone/AAS, and information in the Warning and Precautions section advising prescribers of the importance of measuring serum testosterone concentration if abuse is suspected.

Prescription testosterone products are FDA-approved as hormone replacement therapy for men who have low testosterone due to certain medical conditions. Examples of these conditions include failure of the testicles to produce testosterone because of genetic problems, or damage to the testicles from chemotherapy or infection (FDA, 2016).

Guidelines
Diagnosis of androgen deficiency should include a comprehensive health examination in order to rule out other diseases and use of medications that may impact testosterone synthesis or metabolism. Differences in measurement and intermittent secretion are factors which also effect serum testosterone levels. In addition, testosterone levels are impacted by circadian rhythms where the highest levels occur in the morning. Taking these elements into account, the Endocrine Society recommends obtaining a morning total testosterone level and verification of the results with an additional sample. For individuals with total testosterone levels in the lower range of normal, obtaining a free or bioavailable testosterone level is advised. Individuals should refrain from these lab measurements during periods of illness. To differentiate between primary and secondary hypogonadism, LH and FSH levels are suggested (Bhasin, 2010).

In treating adult males with hypogonadism, current guidelines suggest a preference for prescribing intramuscular or topical testosterone agents over the oral formulations (tablets or capsules) due to the unsatisfactory androgen effects and side effect profile of the oral route. Deciding which particular testosterone therapy to use should be made by the physician and a well-informed patient, taking into consideration factors such benefits versus risks, patient preferences, and pharmacokinetics of the drug formulation. Individuals should be monitored for response to treatment, adverse events and discontinued if there is no response. Although the guidelines suggest initiating therapy with a short-acting formulation, they are silent regarding preference for either topical or injectable testosterone formulations. In regards to adverse events, use of the long acting injectable form could be problematic because of the prolonged wash out period (Bhasin, 2010; Dohle 2015; Petak, 2002; Wang, 2009).

The Endocrine Society Task Force on androgen therapy in women considers androgen deficiency syndrome in healthy women to not be clearly understood and further data is needed. Under these circumstances they do not recommend diagnosis of the syndrome in a healthy female. In general, the Task Force does not recommend the use of testosterone therapy for infertility, cognition, cardiovascular indications, bone health or general well-being. In regards to sexual dysfunction, the group suggests testosterone use should be limited to use in hypoactive sexual desire disorder (HSDD), where evidence demonstrates short-term efficacy and safety of the use of high physiologic dosing of testosterone in the postmenopausal woman with HSDD. Due to the paucity of
data regarding the safety and efficacy of dehydroepiandrosterone (DHEA), the Task Force does not endorse its routine use (Wierman, 2014).

In their Menopause Position Statement, The North American Menopause Society (NAMS, 2012) cites the health risks associated with use of custom compounded bio-identical hormone therapy. NAMS states that in the majority of individuals, an FDA approved hormone replacement is sufficient and avoids the risks associated with compounded preparations. The organization further states it only recommends compounded estrogen replacement therapy in order to avoid allergic reactions to ingredients in FDA approved products (Gass, 2012).

The American Association of Clinical Endocrinologists (AACE) Medical Guidelines for the Clinical Practice for the Diagnosis and Treatment of Menopause do not support the use of compounded bio-identical hormone therapy (Goodman, 2011).

The Endocrine Society has commented that no published studies in peer-reviewed literature demonstrate compounded bio-identical hormone products are more safe or efficacious than FDA approved products. The organization also calls attention to the lack of quality control and safety and efficacy data for compounded preparations. The Society recommends treatment with FDA approved products and does not recommend use of compounded hormone formulations (Stuenkel, 2015; Santen, 2010).

**Quantity Limitations**

FDA recommended dosing supports a quantity limitation of 24 pellets per year while lower level evidence reported in observational and pharmacokinetic studies may indicate a higher quantity (e.g., up to 44) per year (McCullough 2012, Pastuszak 2012). Professional society guidelines do not indicate a specific number of pellets but do suggest an implantation interval of every 3 to 6 months (Bhasin, 2010).

**Experimental, Investigational, Unproven Uses**

Menopausal women may have lower levels of some hormones and experience hot flashes, vaginal dryness, and thin bones. Some physicians prescribe hormones to treat these symptoms, such as estrogen or estrogen with a progestin or progesterone, and some may be compounded and called “bio-identical”. The term “bio-identical” has no defined meaning in any medical or conventional dictionary, and FDA does not recognize the term. In addition, different medical groups define the term differently. Some compounding pharmacies use “bio-identical” as a marketing term to imply that drugs are natural, or have effects identical to those from hormones made by the body. FDA is not aware of credible scientific evidence to support these claims. Compounded products that have identical chemical structures to synthetic hormones can be expected to have the same benefits and risks associated with FDA-approved hormone therapy. Compounded drugs can pose both direct and indirect health risks. Direct health risks include unsafe compounded products. Compounded drugs may be unsafe and compounded drugs made using poor quality compounding practices may be sub- or super-potent, contaminated, or otherwise adulterated. Indirect health risks include the possibility that patients will use ineffective compounded drugs instead of FDA-approved drugs that have been shown to be safe and effective. FDA has approved drugs for use in hormone therapy for menopause symptoms which include products containing only estrogen, products containing only progestin, and products containing estrogen and progestin.

There are no FDA approved, compounded implantable hormone pellets.

**Coding/Billing Information**

**Note:**

1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary for indications outlined in the policy:**

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<tr>
<th>CPT® Codes</th>
<th>Description</th>
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Coverage Policy Number: 1504
Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)

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<td>S0189††</td>
<td>Testosterone pellet, 75 mg</td>
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†Note: Experimental/Investigational/Unproven/Not Covered when used to report subcutaneous implantation of compounded testosterone for any indication.

††Note: Experimental/Investigational/Unproven/Not Covered when used to report estrogen/estrogen derivative pellets (either estrogen/estrogen derivative alone or in combination with testosterone) or implantable progesterone/progestin pellets.

Experimental/Investigational/Unproven/Not Covered when used to report implantable estrogen/estrogen derivative pellets (either estrogen/estrogen derivative alone or in combination with testosterone) or implantable progesterone/progestin pellets:

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<tr>
<td>J3590</td>
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References


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