Name of Policy:
Implantable Hormone Replacement Pellets

Policy #: 444
Category: Pharmacology

Latest Review Date: November 2012
Policy Grade: Effective 05/1/2013:
Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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.
**Description of Procedure or Service:**
Hormone replacement therapy (HRT) can be delivered subcutaneously by implantation of the drug in pellet form in the lower abdomen or buttocks. The procedure is done in a physician’s office with the use of a local anesthetic and a small incision for insertion. The release of the drug continues over a 3-6 month period, eliminating patient compliance with dosing schedules. Since the drug bypasses the GI system and most liver metabolism, bioavailability can be increased. Sustained release can mimic endogenous production achieving therapeutic blood levels. Subcutaneous hormone pellets may be composed of testosterone, estradiol, estrogen, or estrogen in combination with testosterone.

**Testosterone Pellets**
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 known as hypogonadotrophic hypogonadism, includes conditions such as gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury resulting from tumors, trauma, surgery or radiation.

Testosterone hormone replacement can be delivered by mouth, intramuscular injection, topically or subcutaneously by testosterone pellets. Testosterone pellets, Testopel® pellets, have been approved by the U.S Food and Drug Administration (FDA) for the treatment of congenital or acquired androgen deficiency as a result of primary or secondary hypogonadism in males. Each Testopel pellet for subcutaneous implantation contains 75 mg testosterone.

Testosterone pellets are not labeled for use as a treatment for menopausal symptoms or reduced libido. The pharmaceutical references and published literature do not substantiate an off-label indication for these purposes.

Although secondary or tertiary hormonal treatments with androgens are indicated for palliation therapy in post-menopausal women with metastatic breast cancer, subcutaneous testosterone implants are not indicated for these uses and should not be used by females.

**Estrogen**
Estrogen is a hormone that occurs naturally, or is manufactured as a synthetic steroidal or nonsteroidal compound with estrogenic activity. Estrogen is used to treat moderate to severe symptoms of female menopause. Estrogen replacement therapy (ERT) indicates the use of estrogen hormone as a single agent. Estrogen in combination with progestin is called hormone replacement therapy (HRT).

Subcutaneous implantable pellets made up of estradiol, estrogen, or testosterone in combination with estrogen or estradiol has been custom compounded by pharmacists according to physician specifications. However, none of these are FDA approved for U.S. distribution and their safety and efficacy has not been adequately demonstrated in well-designed clinical trials.
**Policy:**

**Effective for dates of service on or after December 29, 2012:**

**Implantable testosterone pellets (Testopel pellets) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following indications in males:

1. As replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, including the following:
   a. Primary hypogonadism, either congenital or acquired. This includes testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome or orchidectomy.
   b. Hypogonadotrophic hypogonadism, either congenital or acquired. This includes idiopathic gonadotropin or LHRH deficiency; or pituitary-hypothalamic injury from tumors, trauma, or radiation.

2. To stimulate puberty in carefully selected males with clearly delayed puberty.

Testosterone pellets should be used as second-line testosterone replacement therapy after oral and IM testosterone other FDA approved prescription testosterone therapies have failed.

The diagnosis of hypogonadism should be documented in the medical record with signs and related symptoms and laboratory studies that show total testosterone < 300 ng/dl or low based on the lab reference standard. and a free testosterone < 20 pg/ml. If the total testosterone is borderline normal, a free testosterone that is low, based on the lab reference standard, may be used to confirm hypogonadism.

**Implantable testosterone pellets (Testopel) do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered **investigational** for all other conditions, including but not limited to the following:

- The treatment of all females, including those with symptoms related to menopause and/or reduced libido.
- Palliation therapy in post-menopausal women with metastatic breast cancer.

**Note:** Implantable testosterone pellets (Testopel) are contraindicated in the following conditions:
- Men with carcinomas of the breast.
- Men with known or suspected carcinomas of the prostate.
- All women, including pregnant women.

**Subcutaneous estrogen or estrogen combined with testosterone or bioidentical hormone pellet therapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for all conditions including the following:

- Females with symptoms related to menopause and/or reduced libido.
Effective for dates of service prior to December 29, 2012:

Implantable testosterone pellets (Testopel pellets) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following indications in males:

1. As replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, including the following:
   a. Primary hypogonadism, either congenital or acquired. This includes testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome or orchidectomy.
   b. Hypogonadotrophic hypogonadism, either congenital or acquired. This includes idiopathic gonadotropin or LHRH deficiency; or pituitary-hypothalamic injury from tumors, trauma, or radiation.

2. To stimulate puberty in carefully selected males with clearly delayed puberty.

Testosterone pellets should be used as second-line testosterone replacement therapy after oral and IM testosterone other FDA approved prescription testosterone therapies have failed.

The diagnosis of hypogonadism should be documented in the medical record with signs and related symptoms and laboratory studies that show total testosterone < 300 ng/dl and a free testosterone < 20 pg/ml.

Implantable testosterone pellets (Testopel) do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational for all other conditions, including but not limited to the following:

- The treatment of all females, including those with symptoms related to menopause and/or reduced libido.
- Palliation therapy in post-menopausal women with metastatic breast cancer.

Note: Implantable testosterone pellets (Testopel) are contraindicated in the following conditions:
- Men with carcinomas of the breast.
- Men with known or suspected carcinomas of the prostate.
- All women, including pregnant women.

Subcutaneous estrogen or estrogen combined with testosterone or bioidentical hormone pellet therapy does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for all conditions including the following:

- Females with symptoms related to menopause and/or reduced libido.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best
medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
Recent publications address the issues related to HRT and the results of different studies. The balance of benefit versus harm using HRT should be influenced by personal preferences, individual risk for specific chronic diseases, and the presence of menopausal symptoms. The physician should discuss the benefits and risks of HRT with each patient before making recommendations. Personal and family history of disease is a critical issue to evaluate in making HRT recommendations to patients.

There are several randomized controlled studies and uncontrolled prospective clinical trials evaluating subcutaneous HRT. Subcutaneous HRT was compared with placebo and with oral and transdermal therapy. The studies had relatively few subjects considering the large number of women candidates for HRT. None of the studies were completely blinded. Symptom relief was largely based on subjective and patient record results. These studies could be subject to bias based on placebo effect. Reported problems with subcutaneous HRT therapy include:

- Problems with pellet removal if the therapy has to be discontinued
- Infection, extrusion and/or discomfort at the insertion site
- Fluctuating blood levels of estrogen
- Dosing is not easily adjusted
- Compliance with cyclical progesterone therapy in hysterectomized women
- The cumulative effect of 2-3 times higher estrogen blood levels over several years not seen with the oral route

While implantable estradiol pellets have been suggested as treatment for symptoms of menopause, there are no FDA-approved, commercially available formulations of implantable estradiol pellets available in the U.S. These formulations of estradiol have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. In 2008, the U.S. Food and Drug Administration’s Fertility and Maternal Health Drugs Advisory Committee unanimously agreed to terminate compassionate investigative new drug (IND) programs for estrogen pellets as a last resort treatment of menopausal disorder. The committee noted “the risk of bleeding and infection, the lack of information on release rates, the difficulty in reversibility of the drug, the increased feasibility of over-dosage of the drug, and the increased risk of non-compliance with safety measures, such as the addition of progestin.

A Task Force from the Endocrine Society published guidelines in October 2006 regarding the therapeutic use of androgens in women. The key recommendations include:

- Recommend against making a diagnosis of androgen deficiency in women at present due to the lack of a well-defined clinical syndrome and normative data on total or free testosterone levels across the lifespan that can be used to define the disorder.
- Recommend against the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacing. Evidence
does exist for short-term efficacy of testosterone in select populations, such as surgically menopausal women.

- Recommend the development of sensitive and specific assays to accurately measure testosterone and free testosterone in women across their lifespan.
- Recommend additional research to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy.

In 2005, the American Congress of Obstetricians and Gynecologists (ACOG) issued a committee opinion #322 regarding “Compounded Bioidentical Hormones”. This statement was reiterated in February 2009 by ACOG. The statement includes the following: Compounded bioidentical hormones are plant-derived hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and can be custom made for a patient according to a physician’s specifications. Unlike drugs that are approved by the FDA to be manufactured and sold in standardized dosages. Most compounded drugs have not undergone rigorous clinical testing for safety or efficacy and issues regarding purity, potency, and quality are a concern. “There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens”.

The North American Menopause Society (NAMS) also supports the FDA and other scientific organizations that have warned about the potential harm from bioidentical hormones. NAMS’ concern arises with the bioidentical hormone medications that are “custom-compounded” recipes prepared by a pharmacist following an individual prescriber’s order for a specific patient. These medications do not have FDA approval because individually mixed recipes have not been tested to prove that the active ingredients are absorbed appropriately or provide predictable levels in blood and tissue. NAMS continues as the other agencies that there is no scientific evidence about the effects of these compounded medications on the body. Salivary and blood testing of hormone levels used by custom compounders is meaningless for midlife women as their hormone levels vary throughout the day and from day to day.

The United States Preventive Services Task Force (USPSTF) has issued the following recommendations about hormone replacement therapy for the prevention of chronic conditions in postmenopausal women:

- The USPSTF recommends against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.
- The USPSTF recommends against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

ACOG recommends that the decision of whether or not to take hormone therapy for menopausal symptoms is highly individualized based on a woman’s health, risk factors and personal wishes. There are a number of FDA approved hormone therapy products available in a variety of formulations. ACOG advises women to talk with their doctor about both the benefits and risk of hormone therapy.

Filko AM, et al (2007), published a retrospective review of the medical records of 258 postmenopausal patients using estradiol and testosterone implants as combined hormone therapy to
evaluate the effects of testosterone on the endometrium after two years of continuous use. Endometrial thickness was measured by ultrasonography. Histology was performed on samples of thickened endometria obtained during hysteroscopy with biopsy. In the 44 patients in whom endometrial thickening was 75mm at the end of the second year of implant use, the most frequent finding at hysteroscopy was polypoid lesion in 61.3% of cases, following by normal uterine cavity in 31.8% of cases and submucous myoma in 6.8%. Histology of the endometrial samples confirmed endometrial polyp in 38.6% of cases, a histologically normal endometrium in 31.8% of cases, simple endometrial hyperplasia in 20.4% of cases, and myoma and atrophic endometrium in 4.5%. It is possible that testosterone may exert its antiproliferative effects on the endometrium but not on polyps in an action similar to that exerted by combined estrogen/progestin therapies. A greater incidence of simple, low-grade endometrial hyperplasia was found in this study compared with studies using continuous estrogen/progestins as the ideal endometrial protection should therefore be reconsidered.

Fennell, et al (2009), reported on testosterone replacement therapy (TRT) for men with organic androgen deficiency. They compared two long-acting depot testosterone (T) products: subdermal T implants (TI) and injectable T undecanoate (TU) for maintenance of TRT. Men with organic androgen deficiency (n=38) undergoing regular TRT were recruited for a 2-period, randomized sequence, cross-over clinical trial without intervening wash-art period of TRT maintenance. For both products, the pharmacokinetics and pharmacodynamics were evaluated using a range of androgen sensitive clinical, laboratory, and quality of life measures as well as preference for ongoing treatment after experiencing both products. The results showed that the two depot T products had distinct pharmacokinetics and were not bioequivalent. There were no consistent clinical differences in a range of pharmacodynamic measures reflecting androgen effects on biochemistry and hematology, muscle mass and strength, and quality of life, mood, and sexual function. The majority (91%) of patients chose TU over TI at study completion. Despite significant pharmacokinetic differences, the two depot T products are clinically interchangeable, but most patients preferred the injectable over the implantable form.

**Key Words:**
Testosterone, Testopel pellets, estrogen, estradiol, androgens, hormone replacement therapy (HRT)

**Approved by Governing Bodies:**
Testosterone pellets received FDA approval August 29, 1986

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable

**Coding:**

CPT  **11980** Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)

HCPCS  **S0189** Testosterone pellet, 75 mg

**References:**


**Policy History:**
Medical Policy Group, August 2010 (3)
Medical Policy Administration Committee, November 2010
Available for comment November 4 – December 20, 2010
Medical Policy Group, June 2011; Wording change in Policy Section
Medical Policy Administration Committee, June 2011
Available for comment June 8 – July 25, 2011
Medical Policy Group, August 2011: Updated and removed pellets to be second-line treatment based on comments
Medical Policy Administration Committee, September 2011
Available for comment September 2 through October 17, 2011
Medical Policy Group, November 2012 (3): Policy statement updated related to diagnosis of hypogonadism documentation and updated references to support policy change.
Medical Policy Administration Committee, November 2012
Available for comment November 14 through December 28, 2012
Medical Policy Group, May 2013: Effective May 1, 2013 Active Policy but no longer scheduled for regular literature reviews and updates

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.