Prior Authorization Review
Panel MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Aetna Better Health  Submission Date: 11/01/2018

Policy Number: 0345  Effective Date:  Revision Date:

Policy Name: Implantable Hormone Pellets

Type of Submission – Check all that apply:
- New Policy
- Revised Policy*
- Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

CPB 0345 Implantable Hormone Pellets

Clinical content was last revised 06/05/2015. Additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

Revision and Update History since last PARP submission:
04/13/2018 - This CPB has been updated with additional coding.
08/21/2018 - This CPB has been updated to state that consecutive testing of fasting serum testosterone levels refer to testing in succession; not consecutive days of testing.
03/28/2019 – Next tentative scheduled review date by Corporate

Name of Authorized Individual (Please type or print):

Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

www.aetnabetterhealth.com/pennsylvania  Updated 08/21/2018
Implantable Hormone Pellets

Number: 0345

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Policy

I. Estrogen:

Aetna considers implantable estradiol pellets experimental and investigational because they have been shown to produce unpredictable and fluctuating serum concentrations of estrogen.

II. Testosterone:

Aetna considers implantable testosterone pellets (Testopel pellets) medically necessary for any of the following indications:

A. Delayed male puberty; or
B. Female to male gender reassignment; or
C. Hypogonadotropic hypogonadism (congenital or acquired) with low serum testosterone (see appendix): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-
hypothalamic injury from tumors, trauma, or radiation;

or

D. Primary hypogonadism (congenital or acquired) (androgens) with low serum testosterone (see appendix): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchietomy (also called orchidectomy), Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals

Aetna considers implantable testosterone pellets experimental and investigational for the following (not an all-inclusive list) because their effectiveness for indications other than the ones listed above has not been established:

- Hypogonadism due to aging
- Idiopathic hypogonadism (not due to disorders of the testicles, pituitary gland or brain)
- Male menopause
- Treatment of symptoms associated with menopause (as this use remains unlabeled and unsubstantiated)

*Note: Documentation of low serum testosterone is not required for bilateral orchietomy.

III. Progestin/Progesterone:

Aetna considers progestin/progesterone pellets experimental and investigational for the treatment of dysmenorrhea and erythema nodosum because their effectiveness for these indications has not been established.

See

CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists (/500_599/0501.html)
Background

Implantable Estrogen

While implantable estradiol pellets have been suggested as treatment for symptoms of menopause, there are no United States Food and Drug Administration (FDA)-approved, commercially available formulations of implantable estradiol pellets available in the United States. These formulations of estradiol have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. The FDA'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, difficulty in reversibility of the drug, increased feasibility of over-dosage of the drug, and increased risk of non-compliance with safety measures [such as] the addition of progestin.”

Testosterone Implants

Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (e.g., beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. Low serum testosterone concentrations due to inadequate secretion of testosterone is associated with male hypogonadism. Symptoms include decreased sexual desire with or without impotence, fatigue, and mood disturbances.

Implantable testosterone pellets may be indicated as second-line testosterone replacement therapy for males. Testosterone implants (Testopel Pellets) are commercially available in the
United States. Testopel (testosterone) is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Androgens are primarily indicated in males as replacement therapy when congenital or acquired endogenous androgen absence or deficiency is associated with primary or secondary hypogonadism. Primary hypogonadism includes conditions such as: testicular failure due to cryptorchidism, bilateral torsion, orchitis, or vanishing testis syndrome; inborn errors in testosterone biosynthesis; or bilateral orchidectomy. Hypogonadotropic hypogonadism (secondary hypogonadism conditions include gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury as a result of surgery, tumors, trauma, or radiation, and are the most common forms of hypogonadism seen in older adults.

Testosterone is available as Testopel in 77mg pellets (75mg testosterone) for subcutaneous implantation. If testosterone implants are to be used for treatment of androgen deficiency due to primary or secondary hypogonadism, the usual adult dosage is 150 to 450 mg subcutaneously every 3 to 4 months, or, in some cases, as long as 6 months. Dosage adjustment is needed to accommodate individual clinical requirements for such life changes as induction of puberty, development of secondary sexual characteristics, impotence due to testicular failure, or infertility due to oligospermia.

For treatment of delayed male puberty, a 6-month or shorter course of androgen is indicated for induction of puberty in patients with familial delayed puberty, a condition characterized by spontaneous, non-pathologic, late-onset puberty, if the patient does not respond to psychological treatment. If subcutaneous testosterone implants are to be used, the usual dosage is in the lower range of that listed above. Low-doses are used initially and increased gradually as puberty progresses.
Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism (FDA, 2015). However, the FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established (FDA, 2015).

The FDA advises that health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests (FDA, 2015). Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy. Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as chest pain, shortness of breath or trouble breathing, weakness in one part or one side of the body, or slurred speech.

The FDA is requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications (FDA, 2015). The FDA is also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. The FDA cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone (FDA, 2015).

Based on the available evidence from studies and expert input from an FDA Advisory Committee meeting, the FDA has concluded that there is a possible increased cardiovascular
risk associated with testosterone use (FDA, 2015). 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 (FDA, 2015).

Testopel has potential for abuse (Schedule CIII).

Testopel must not be used in women as testosterone exposure during pregnancy has been reported to be associated with fetal abnormalities.

Pellet implantation is much less flexible for dosage adjustment than is oral administration, intramuscular injections of oil solutions, or aqueous suspensions and, therefore, great care should be used when estimating the amount of testosterone needed.

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 75mg pellets for each 25mg testosterone propionate required weekly. Thus when a patient requires injections of 75mg per week, it is usually necessary to implant 450mg (6 pellets). With injections of 50mg per week, implantation of 300mg (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.

Filho et al (2007) retrospectively reviewed the medical records of 258 post-menopausal patients using estradiol and testosterone implants as combined hormone therapy to evaluate the effects of testosterone on the endometrium after
2 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 greater than 5 mm at the end of the second year of implant use, the most frequent finding at hysteroscopy was polypoid lesion in 61.3% of cases, followed 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 anti-proliferative 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/progestin regimens. The use of progestins as the ideal endometrial protection should therefore be re-considered.

Fennell and colleagues (2010) compared the 2 long-acting depot testosterone (T) products -- subdermal T implants (TI) and injectable T undecanoate (TU) -- for maintenance of testosterone replacement therapy (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-out period of TRT maintenance. For both depot T products, their 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 experience of both products. The 2 depot T products had distinct pharmacokinetics and were not bioequivalent. However, there were no consistent clinical differences in a comprehensive 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 subjects chose TU over TI at study completion. The authors concluded that despite significant pharmacokinetic differences, the 2 depot T products are clinically interchangeable allowing for choice dependent on patient and physician delivery preference in practice; but most patients preferred the injectable over the implantable form.

Reis and Abdo (2014) stated that with advancing age, there is an increase in the complaints of a lack of a libido in women and erectile dysfunction in men. The effectiveness of phosphodiesterase type 5 inhibitors (PDE5i), together with their minimal side effects and ease of administration, revolutionized the treatment of erectile dysfunction. For women, testosterone administration is the principal treatment for hypoactive sexual desire disorder. These investigators evaluated the use of androgens in the treatment of a lack of libido in women, comparing 2 periods, i.e., before and after the advent of the PDE5i. These researchers also analyzed the risks and benefits of androgen administration. They searched the Latin-American and Caribbean Health Sciences Literature, Cochrane Library, Excerpta Medica, Scientific Electronic Library Online, and Medline (PubMed) databases using the search terms disfunção sexual feminina/female sexual dysfunction, desejo sexual hipoativo/female hypoactive sexual desire disorder, testosterona/testosterone, terapia androgênica em mulheres/androgen therapy in women, and sexualidade/sexuality as well as combinations thereof. They selected articles written in English, Portuguese, or Spanish. The authors concluded that after the advent of PDE5i, there was a significant increase in the number of studies aimed at evaluating the use of testosterone in women with hypoactive sexual desire disorder. However, they stated that the risks and benefits of testosterone administration have yet to be clarified.
Corona et al (2014) noted that the role of testosterone supplementation (TS) as a treatment for male sexual dysfunction remains questionable. These researchers attempted a meta-analysis on the effect of TS on male sexual function and its synergism with the use of PDE5i. An extensive Medline, Embase, and Cochrane search was performed. All randomized controlled trials (RCTs) comparing the effect of TS versus placebo or the effect of TS as add on to PDE5is on sexual function were included. Data extraction was performed independently by 2 of the authors, and conflicts resolved by the third investigator. Out of 1,702 retrieved articles, 41 were included in the study. In particular, 29 compared TS versus placebo, whereas 12 trials evaluated the effect of TS as add on to PDE5is. Testosterone supplementation is able to significantly ameliorate erectile function and to improve other aspects of male sexual response in hypogonadal patients. However, the presence of possible publication bias was detected. After applying "trim and fill" method, the positive effect of TS on erectile function and libido components retained significance only in RCTs partially or completely supported by pharmaceutical companies (confidence interval [CI]: 0.04 to 0.53 and 0.12 to 0.52, respectively). In addition, these researchers reported that TS could be associated with an improvement in PDE5i outcome. These results were not confirmed in placebo-controlled studies. The majority of studies, however, included mixed eugonadal/hypogonadal subjects, thus imparting uncertainty to the statistical analyses. The authors concluded that TS plays positive effects on male sexual function in hypogonadal subjects. The role of TS is uncertain in men who are not clearly hypogonadal. The apparent difference between industry-supported and independent studies could depend on trial design more than on publication bias. They stated that new RCTs exploring the effect of TS in selected cases of PDE5i failure that persistently retain low testosterone levels are advisable.
Fui et al (2014) stated that with increasing modernization and urbanization of Asia, much of the future focus of the obesity epidemic will be in the Asian region. Low testosterone levels are frequently encountered in obese men who do not otherwise have a recognizable hypothalamic-pituitary-testicular (HPT) axis pathology. Moderate obesity predominantly decreases total testosterone due to insulin resistance-associated reductions in sex hormone binding globulin. More severe obesity is additionally associated with reductions in free testosterone levels due to suppression of the HPT axis. Low testosterone by itself leads to increasing adiposity, creating a self-perpetuating cycle of metabolic complications. Obesity-associated hypotestosteronemia is a functional, non-permanent state, which can be reversible, but this requires substantial weight loss. While TRT can lead to moderate reductions in fat mass, obesity by itself, in the absence of symptomatic androgen deficiency, is not an established indication for TRT. The authors concluded that TRT may lead to a worsening of untreated sleep apnea and compromise fertility. Whether TRT augments diet- and exercise-induced weight loss requires evaluation in adequately designed RCTs.

Cai et al (2014) evaluated the metabolic effects of TRT on hypogonadal men with type 2 diabetes mellitus (T2DM). These investigators performed a literature search using the Cochrane Library, EMBASE and PubMed. Only RCTs were included in the meta-analysis; 2 reviewers retrieved articles and evaluated the study quality using an appropriate scoring method. Outcomes including glucose metabolism, lipid parameters, body fat and blood pressure were pooled using a random effects model and tested for heterogeneity. These researchers used the Cochrane Collaboration's Review Manager 5.2 software for statistical analysis. A total of 5 RCTs including 351 participants with a mean follow-up time of 6.5 months were identified that strictly met the eligibility criteria. A meta-analysis of the extractable data showed that testosterone reduced fasting plasma glucose levels (mean difference (MD):
-1.10; 95 % CI: -1.88 to -0.31), fasting serum insulin levels
(MD: -2.73; 95 % CI: -3.62 to -1.84), HbA1c % (MD: -0.87; 95 %
CI: -1.32 to -0.42) and triglyceride levels (MD: -0.35; 95 %
CI: -0.62 to -0.07). The testosterone and control groups
demonstrated no significant difference for other outcomes.
The authors concluded that TRT can improve glycemic control
and decrease triglyceride levels of hypogonadal men with
T2DM. However, they stated that considering the limited
number of participants and the confounding factors in this
systematic review; additional large, well-designed RCTs are
needed to address the metabolic effects of TRT and its long-
term influence on hypogonadal men with T2DM.

**Progesterone Pellets**

An UpToDate review on “Treatment of primary dysmenorrhea
in adult women” (Smith and Kaunitz, 2014) does not mention
the use of progestin pellet as a management option.

An UpToDate review on “Erythema nodosum” (Shojania,
2014) does not mention the use of progestin/progesterone as
a management option.

**Appendix**

Androgen deficiency is indicated by either 2 consecutive low
total (free plus protein-bound) fasting serum testosterone
levels (below the testing laboratory's normal reference range
or below 300 ng/dL), or for persons with low normal total
fasting serum testosterone levels (above 300 ng/dL but below
400 ng/dL), 2 consecutive low free or bioavailable fasting
serum testosterone levels (below the testing laboratory's
normal reference range or less than 225 picomoles per liter
(pmol/L) (6 ng/dL) if reference ranges are not available).
Two consecutive fasting total serum testosterone levels are
required to determine medical necessity of testosterone
replacement, or 2 consecutive free or bioavailable fasting
serum testosterone levels if total testosterone is in the low normal range. Two morning samples drawn between 7:00 a.m. and 10:00 a.m. obtained on different days are required. (One fasting total serum testosterone level is sufficient for persons with severe deficiency (less than 150 ng/dL). Testosterone levels should not be measured during acute or subacute illness.

Notes:

Reference laboratories ranges should be used to document testosterone levels. A laboratory reference range is defined as the set of values 95 % of the normal population falls within (that is, 95 % prediction interval).

Consecutive testing of fasting serum testosterone levels refer to testing in succession; not consecutive days of testing.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>11980</td>
<td>Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin) [covered for testosterone only - not estradiol]</td>
</tr>
<tr>
<td>11981</td>
<td>Insertion, non-biodegradable drug delivery implant [not covered when used to implant progestin/ progestosterone pellets]</td>
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Other CPT codes related to the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>80414</td>
<td>Chorionic gonadotropin stimulation panel; testosterone response</td>
</tr>
<tr>
<td>80415</td>
<td>estradiol response</td>
</tr>
<tr>
<td>84402</td>
<td>Testosterone; free</td>
</tr>
<tr>
<td>84403</td>
<td>total</td>
</tr>
<tr>
<td>84410</td>
<td>Testosterone; bioavailable, direct measurement (eg, differential precipitation)</td>
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</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>S0189</td>
<td>Testosterone pellet, 75mg</td>
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ICD-10 codes covered if selection criteria are met:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>E23.0</td>
<td>Hypopituitarism [hypothalamic hypogonadism] [not covered for androgen deficiency due to aging or idiopathic hypogonadism not due to disorders of the testicles, pituitary gland or brain]</td>
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<tr>
<td>E29.1</td>
<td>Testicular hypofunction [primary] [not covered for androgen deficiency due to aging or idiopathic hypogonadism not due to disorders of the testicles, pituitary gland or brain]</td>
</tr>
<tr>
<td>E30.0</td>
<td>Delayed puberty [congenital or acquired endogenous androgen absence or deficiency]</td>
</tr>
<tr>
<td>F64.0</td>
<td>Gender identity disorders</td>
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<tr>
<td>F64.9</td>
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</tr>
<tr>
<td>Z87.890</td>
<td>Personal history of sex reassignment</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in CPB:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>L52</td>
<td>Erythema nodosum</td>
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<tr>
<td>N50.89</td>
<td>Other specified disorders of male genital organs [male menopause]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>N91.0 -</td>
<td>Disorders of menstruation and other abnormal bleeding</td>
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<td>N93.9</td>
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<td>N94.4 -</td>
<td>Dysmenorrhea</td>
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<td>N94.6</td>
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<tr>
<td>N95.0 -</td>
<td>Menopausal and other perimenopausal disorders</td>
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<td>N95.9</td>
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<tr>
<td>Z85.43</td>
<td>Personal history of malignant neoplasm of ovary</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

7. Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of...


17. F-D-C- Reports Inc. Estrogen pellets availability under compassionate INDs should be discontinued as a last resort treatment for menopausal symptoms -- FDA advisory committee. The Pink Sheet. 1988;50(4).


29. Smith RP, Kaunitz AM. Treatment of primary dysmenorrhea in adult women. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2014.

30. Shojania KG. Erythema nodosum. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2014.


36. U.S. Food and Drug Administration (FDA). FDA cautions about using testosterone products for low testosterone due to aging; Requires labeling change to

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number:
0345 Implantable Hormone Pellets

There are no amendments for Medicaid.