Implantable Hormone Pellets

Policy # 00073
Original Effective Date: 01/26/2004
Current Effective Date: 06/18/2014

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:

- Hormone pellet implantation is being used in males with congenital or acquired endogenous androgen absence or deficiency 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 orchiectomy. 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.); 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 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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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
There are no FDA-approved commercially available formulations of implantable estradiol pellets available in the United States. The FDA’s Fertility and Maternal Health Drugs Advisory Committee terminated compassionate investigative new drugs program for estrogen pellets as a last resort treatment of menopausal disorder noting:

- The risk of bleeding and infection
- The lack of information on release rates
- Difficulty in reversibility of the drug
- Increased feasibility of overdose
- Age
- Increased risk of non-compliance with safety measures (such as the addition of progestin)

The FDA has approved implantable testosterone pellets as replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone in males. The FDA does not approve testosterone pellets for use in females.

The combination drug therapy of estrogen/testosterone pellets is used as HRT for menopausal and post-menopausal females.

The FDA recommendations are based on inadequate peer review literature that shows safety and efficacy in the use of implantable hormone pellets in women.

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
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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. Testosterone replacement therapy 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

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 2013 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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*Procedural Terminology* which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

*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:

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<th>Code Type</th>
<th>Code</th>
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<td>CPT</td>
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<td>ICD-9 Procedure</td>
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**Policy History**

Original Effective Date: 01/26/2004
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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.

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Next Scheduled Review Date: 06/2015

*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.