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Policy Effective Date	**07/15/2024**
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Hormone Replacement Therapies (HRT) Using Implanted Pellets for Women and Delayed Puberty

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Related Policies (if applicable)
SUR717.001: Gender Assignment Surgery and Gender Reassignment Surgery with Related Services
RX501.076: Testosterone Replacement Therapies
RX501.063: Compounded Drug Products

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-

reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery with Related Services.

This policy addresses hormone replacement treatment for women and for delayed puberty only. This policy does not address the use of a non-biodegradable drug delivery implant when utilized for purposes of contraception.

- **For the associated policy related to testosterone replacement treatment for men, please see Testosterone Replacement Therapies – RX501.076.**
- **For policy addressing bioidentical hormone replacement therapy for any gender, please see Compounded Drug Products – RX501.063.**

Hormone replacement therapy (HRT) using implanted testosterone pellets **is considered experimental, investigational and/or unproven** for all non-FDA (U.S. Food and Drug Administration) approved indications including, but not limited to female menopause.

HRT using implanted estrogen/estradiol pellets **is considered experimental, investigational and/or unproven** including, but not limited to female menopause.

HRT using implanted testosterone pellets (such as Testopel®) **is considered not medically necessary** for the treatment of delayed puberty not resulting from hypogonadism.

NOTE: Some HRT preparations may be compounded into a combined testosterone and estrogen/estradiol formula for use in implanted pellets.

Policy Guidelines

None.

Description

Testosterone and estrogen are among the class of sexual hormones that regulate the growth and function of reproductive organs or stimulate the development of secondary sexual

characteristics. Sexual hormone disorders occur when there is either an overproduction or underproduction responsible for sexual characteristics and development. In females, the primary female hormone is estrogen, which is produced by the ovaries. In males, the main male hormone is testosterone, which is produced in the testicles.

Background

Menopause

Menopause naturally occurs as a biological process when a woman's ovaries stop producing hormones, resulting in cessation of fertility. Menopause is defined as beginning 12 months following the last menstrual cycle. However, there may be months or years of symptoms leading up to menopause, known as perimenopause (transitional menopause). Menopause generally happens during the woman's 40's and 50's, with the average age of 51 years old. (1)

Each woman's experience of menopause is different. Many women report no physical changes during perimenopause except irregular menstrual periods that stop when menopause is reached. Other women experience symptoms of hot flashes, night sweats (heavy sweating from hot flashes at night, often disturbing sleep), and thinning and drying of vaginal tissue causing painful sex. How severe these body changes are, varies from woman to woman, but for the most part these changes are perfectly natural and normal. (1)

Delayed Puberty

The time in one's life when sexual maturity takes place is known as puberty. The physical changes that mark puberty typically begin in girls between ages 8 and 13 and in boys between ages 9 and 14. Precocious puberty is a condition that occurs when sexual maturity begins earlier than normal. Precocious (meaning prematurely developed) puberty begins before age 8 for girls and before age 9 for boys. Delayed puberty is the term for a condition in which the body's timing for sexual maturity is later than the normal range of ages. (2)

Many children with delayed puberty will eventually go through an otherwise normal puberty, just at a late age. Other children have a long-lasting condition known as hypogonadism in which the sex glands (the testes in men and the ovaries in women) produce few or no hormones. For example, hypogonadism can occur in girls with Turner syndrome or in individuals with hypogonadotropic hypogonadism, which occurs when the hypothalamus produces little to no gonadotropin-releasing hormone (GnRH). (2)

Hormone Replacement Treatments

Estrogen therapy is used primarily to treat the symptoms of menopausal and postmenopausal women and to decrease the risk of osteoporosis and cardiovascular disease. Estrogen replacement therapy has also been investigated for the prevention of menstrual migraine headaches and to prevent or reduce neural degeneration in Alzheimer's disease and Parkinson's disease.

Typical methods of estrogen administration include oral tablets, intramuscular injections, vaginal creams, and transdermal patches. Estrogen pellets are sometimes combined with

testosterone implants to enhance the effects of hormone replacement therapy (HRT). Subcutaneous doses of testosterone can be delivered 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 three to six-month period, eliminating patient compliance with dosing schedules. Since the drug bypasses gastrointestinal and most liver metabolism, bioavailability can be increased.

The treatment for delayed puberty depends on its cause. An adolescent who is naturally late in developing needs no treatment, although if the adolescent is severely stressed by the lack of development or development is extremely delayed, some doctors may give supplemental sex hormones to begin the process sooner. If boys show no sign of puberty or bone maturation by age 15, they may be given a 4- to 6-month course of testosterone injections. Testosterone induces puberty, causes the development of some masculine characteristics (virilization), and does not jeopardize adult height potential. When an underlying disorder is the cause of delayed puberty, puberty usually proceeds once the disorder has been treated. Genetic disorders cannot be cured, although replacing hormones may help sex characteristics develop. Surgery may be needed for adolescents with tumors. (3)

Regulatory Status

There are numerous different U.S. Food and Drug Administration (FDA)–approved formulations of testosterone and estrogens that are available for replacement therapy. For the majority of delivery preparations, FDA approval was granted on the ability to increase levels to the normal range, and not on demonstration of beneficial clinical outcomes. However, when it comes to subcutaneous implanted testosterone pellets, the FDA has Testopel® listed without an approved label. Testopel® is produced by several manufacturers, including Bartor Pharmacal, Rye, NY. (4) The recommended dosing range for Testopel® is 150 to 450 mg every 3 to 6 months. For 75-mg pellets, this would correspond to implant of 2 to 6 pellets every 3 to 6 months. The dosing interval is individualized, as some patients will require re-dosing as early as every 3 months while others may not require re-dosing for up to 6 months. There is not an FDA-approved label for Testopel®; however, the Testopel® official website includes full prescribing information. The manufacturer mentioned in the Testopel® official website is Endo Pharmaceuticals Inc., Malvern, PA. (5)

Currently no implantable estrogen pellets have received FDA approval. The FDA has published information for prescribers and patients providing information, including the hazards and misconceptions for these types of compounded pellets. (6)

Rationale

This policy was originally created in 1990 based upon U.S. Food and Drug Administration (FDA) available information. The most recent literature and FDA labeled search was performed through May 2024. No FDA-approved labels were identified through the FDA website. The following is a summary of key literature to date.

Menopause

There have been several randomized controlled trials (RCTs) and uncontrolled clinical trials evaluating implantable estradiol pellets. (7-16) These implants have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. The FDA's Fertility and Maternal Health Drugs Advisory Committee (January 1988) unanimously agreed to terminate compassionate investigative new drug (IND) programs for estrogen pellets as a last-resort treatment of menopausal disorder. (6) The committee noted "the risk of bleeding and infection, the lack of information on release dates 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."

Estradiol therapy was compared with placebo and with oral and transdermal therapy. (7-16) The studies had relatively few subjects considering the large number of women candidates for hormone replacement therapy (HRT). None of the studies were completely blinded. Symptom relief was largely based on subjective and patient-reported results. These studies could be subject to bias based on placebo effect. Only three studies that measured the effect of estrogen implant on bone density directly compared estrogen replacement therapy implants with other methods of estrogen administration.

In 2012, the North American Menopause Society (NAMS) updated its 2010 recommendations regarding the use of postmenopausal HRT based on evidence accumulated subsequent to the previous report. (17) In the decade since the first publication (20) of the results from the Women's Health Initiative (21), the society has accumulated evidence to indicate that multiple factors influence the effects of hormone therapy, including the type of estrogen used, the way the hormones are given, the age and recency of menopause of the woman taking the medication. These factors also determine the risks associated with hormone therapy.

The North American Menopause Society (NAMS) Position Statement published in 2012 was updated in 2017 and again in 2022, highlighted the following findings: (18, 19)

- "Hormone therapy is the most effective treatment for vasomotor and genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture.
- Risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation.
- For women aged younger than 60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome vasomotor syndrome and for the prevention of bone loss or fracture. Based on the Women's Health Initiative randomized controlled trials, longer duration may be more favorable for estrogen therapy than for estrogen-progestogen therapy.
- For women who initiate hormone therapy more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for

younger women because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.
- For genitourinary syndrome of menopause symptoms not relieved with nonhormone therapies, low-dose vaginal estrogen therapy or other government-approved therapies (e.g., vaginal DHEA or oral ospemifene) are recommended."

This statement acknowledges that it is impossible to generate guidelines that can be used for all women. (18) The decision to use hormone therapy must be made on a case-by-case basis, where the clinician takes into consideration the severity of the woman's symptoms and their effect on her quality of life, as well as her personal risk factors for complications associated with hormone therapy (i.e., venous thrombosis, cardiovascular disease, stroke, and breast cancer). Overall, these findings are reassuring. While some women, specifically older postmenopausal women and those with certain risk factors may not be good candidates for hormone therapy, estrogen remains a viable treatment option for many women with bothersome menopausal symptoms.

NAMS recommends that bioidentical hormone therapy (BHT) products include a patient package insert identical to that required for products that have government approval. (17) In the absence of efficacy and safety data for BHT, the generalized benefit-risk ratio data of commercially available hormone therapy (HT) products should apply equally to BHT. For most women, government-approved HT will provide appropriate therapy without the risks of custom preparations. Therefore, NAMS does not generally recommend compounded estrogen-progestogen therapy (EPT) or estrogen therapy (ET) unless necessary because of allergies to ingredients contained in government-approved products. In 2022, NAMS updated the Hormone Therapy Position Statement and continues to indicate the following: (18, 19) "Compounded hormone therapies are prepared by a compounding pharmacist using a provider's prescription and may combine multiple hormones (estradiol, estrone, estriol, dehydroepiandrosterone [DHEA], testosterone, progesterone), and use untested, unapproved combinations or formulations, or be administered in nonstandard (untested) routes such as subdermal implants, pellets, or troches."

According to the American College of Obstetricians and Gynecologists (ACOG) (2014, reaffirmed 2018) Practice Bulletin for the Management of Menopause, testosterone poses no benefit, except for improved sexual satisfaction, but comes with multiple risks. (22) As for estrogen replacement, ACOG's guidance stated, "Too little evidence supports benefit of compounded bioidentical hormones."

The FDA has ruled that some compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by clinical trial data and considered to be false and misleading. (23) Pharmacies have been instructed not to use estriol without an investigational new drug authorization. The FDA also states that there is no scientific basis for using saliva testing to adjust hormone levels.

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 due to lack of controlled evaluations.

Delayed Puberty

In a discussion on delayed puberty, the American Academy of Pediatrics (AAP) stated that most cases of delayed puberty are simply variants of normal development and not cause for alarm. (24, 25)

According to the manufacturer's product label for Testopel®, as there is no FDA-approved label; androgen replacement may be used to stimulate puberty in carefully selected males who have a familial pattern of delayed puberty that is not secondary to a pathological disorder. (5) Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. Among the contraindications for children, exposure to testosterone may accelerate bone maturation without producing the compensatory gain in linear growth, which can compromise adult stature, and may compromise growth height by affecting bone growth to prematurely close epiphyseal centers preventing bone growth and maturation.

Ongoing and Unpublished Clinical Trials

There are no known clinical trials that would influence the coverage of this medical policy.

Summary of Evidence

With the lack of U.S. Food and Drug Administration (FDA) approved labeling and scant amount of scientific literature for the safety and utility in short- or long-term therapy, hormone replacement therapy using testosterone and/or estrogen subcutaneously implanted pellets is considered experimental, investigational, and/or unproven to treat female menopause or delayed puberty.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	11980, 11981, 11982, 11983
HCPCS Codes	S0189, G0516, G0517, G0518

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/15/2024	Document updated with literature review. Coverage unchanged. References 1-3 added and some updated.
05/01/2023	Reviewed. No changes.
09/15/2022	Document updated with literature review. Coverage unchanged. Reference 14 added and some updated.
06/15/2021	Document updated with literature review. Coverage unchanged. Some references updated; no new references added.
03/15/2020	Reviewed. No changes.
07/15/2018	Document updated with literature review. Coverage unchanged. References 13 and 18 added.
04/15/2017	Reviewed. No changes.
04/01/2016	Document updated with literature review. Coverage unchanged.
11/01/2015	Reviewed. No changes.
10/01/2014	Document updated with literature review. The following NOTE was added to the coverage: Some hormone replacement therapy preparations may be compounded into a combined testosterone and estrogen/estradiol formula for use in implanted pellets. Coverage statements and information regarding the treatment of primary hypogonadism and hypogonadotropic hypogonadism for men moved to a new policy document Testosterone Replacement Therapies, RX501.076. Description, Rationale, and References significantly revised and reorganized. Otherwise, coverage unchanged. Title changed from Subcutaneous Hormone Implants.
05/01/2012	Document updated with literature review, No change in coverage. Rationale updated with 2012 North American Menopause Society Position Statement recommendations.
05/15/2010	Document updated with literature review. The title was changed from Estradiol Pellets. The following was added: Subcutaneous testosterone pellets (Testopel™) may be considered medically necessary for the following Food and Drug Administration (FDA) approved indications in males: primary hypogonadism, and hypogonadotrophic hypogonadism . Subcutaneous testosterone pellets (Testopel™) are considered not medically necessary for treatment of delayed puberty not resulting from hypogonadism.
01/01/2010	Revised/updated entire document. Testosterone subcutaneous pellets are now considered a convenience item and not medically necessary. Medical policy title changed from Estradiol Pellets.
08/15/2009	Routine review with literature search, no change in coverage. This policy is no longer scheduled for routine literature review and update.
07/15/2007	Revised/updated entire document
10/01/2005	Revised/updated entire document
01/01/2005	Revised/updated entire document
02/01/2002	Revised/updated entire document
05/01/2000	Revised/updated entire document

05/01/1996	Revised/updated entire document
06/01/1991	Revised/updated entire document