Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND071.0225	**ENDOCRINE & METABOLIC DRUGS** **MEDICAL HORMONE THERAPY** See Table 1 for Medications
Effective Date: 3/1/2025	**Review/Revised Date**: 08/15, 03/16, 07/16, 03/17, 3/18, 05/18, 07/18, 01/19, 02/19, 03/19, 02/20, 03/21, 07/21, 03/22, 03/23, 05/23, 02/24, 09/24, 12/24 (JLS)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B – criteria based on Local Coverage Determination - L36569

POLICY CRITERA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of testosterone replacement therapy (new starts), must meet all the following criteria
    a. One of the following confirmed diagnoses:
        i. Diagnosis of gender dysphoria or gender incongruence OR
        ii. Diagnosis of clinical hypogonadism, defined as meeting the following (1-3):
            1) Documentation (including results from laboratory tests) of at least two separate serum testosterone levels taken on two different days in the morning (when testosterone secretion is highest), and / or two morning levels of "free" or bioavailable testosterone) indicating low testosterone levels
            2) Documentation (including results from laboratory tests) of one of the following:
                a) Elevated luteinizing hormone (LH) or follicle-stimulating hormone (FSH) levels indicating primary hypogonadism
                b) For patients with low luteinizing hormone (LH) or follicle-stimulating hormone (FSH) levels, documentation that an assessment of pituitary

disease and other chronic diseases was made before making a diagnosis of age-related low testosterone

3) Documentation in chart notes of the presence of low testosterone associated symptoms (such as decreased energy, sleep disturbances, anemia, hot flushes, etc)

b. Documented trial and failure (defined as inability to reach therapeutic levels or fluctuations in levels resulting in symptoms) of both of the following:
   i. Generic formulary topical testosterone (such as generic topical testosterone 1% or generic topical testosterone 1.62% pump); and
   ii. Generic injectable testosterone cypionate.

2. For patients established on the requested testosterone replacement therapy (within the previous year): Documentation of positive response to therapy and ongoing monitoring of hormone levels
3. For estrogen replacement therapy: The use of a subcutaneous pellet formations of estrogen is considered investigational for all indications.

Note that compounded testosterone pellets are not FDA approved and are not covered.

EXCLUSION CRITERIA:

- Use for improvement of sexual signs and symptoms (such as decreased libido, sexual dysfunction)
- Use in patients with breast cancer or untreated prostate cancer
- Compounded hormones for pellet insertion that are not FDA approved

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMIT:
Testopel® is limited to a maximum of six pellets per insertion
Medicare may only cover the number of pellets actually implanted in the patient (maximum of six pellets); wastage is not covered. Use of additional pellets may be paid on appeal if the documentation supports medical necessity as determined by the FDA approved drug label and the service complies with all Medicare requirements as indicated above.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND071	ENDOCRINE & METABOLIC DRUGS HORMONE REPLACEMENT THERAPY See Table 1 for Medications

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Each testosterone replacement therapy (TRT) product is approved for use in adult males for conditions associated with a deficiency or absence of endogenous testosterone, commonly referred to as hypogonadism. The condition is further classified into primary hypogonadism, failure of the testicles to produce testosterone, and secondary (hypogonadotropic) hypogonadism, central defects in the hypothalamus or pituitary gland, both leading to low testosterone levels. In primary hypogonadism, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are generally at normal or elevated levels; where as in secondary hypogonadisms levels are decreased. There are various administration routes available for TRT, including transdermal patch, topical gels, buccal formulations, implantable pellets and intramuscular injections (short & long acting) of which all have been proven effective in increasing testosterone levels.

Note: All TRT products are Drug Enforcement Administration (DEA) Controlled Substance Class III

FDA APPROVED INDICATIONS:

Replacement therapy in congenital or acquired conditions associated with a deficiency or absence of endogenous testosterone, such as:

- Primary hypogonadism: testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.
- Secondary (hypogonadotropic) hypogonadism: idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

POSITION STATEMENT:

Testosterone Replacement Therapy (TRT)

- There is no evidence demonstrating any one TRT product is safer or more effective than other therapeutic alternatives. All products were proven effective based on pharmacokinetic data.
- Total serum testosterone level must be measured to confirm diagnosis of hypogonadism.
- According to the 2018 Endocrine Society Guidelines: For {total serum testosterone} laboratories that are not CDC certified and do not participate in an accuracy-based quality control program, the reference range may vary considerably depending on the assay and reference population used. Using the lower limit of the range established in local laboratories may not accurately identify men with hypogonadism.
- A harmonized reference range for free testosterone (FT) has not been established, so reference ranges may vary considerably depending on the specific equilibrium dialysis method or the algorithm used to calculate FT. Therefore, until a harmonized reference range is established, the lower limits established by the laboratory may be used.
- Testosterone exhibit diurnal variation levels, with peak levels in the morning and varying levels throughout the day. A confirmed diagnosis of hypogonadism must be measured by morning serum testosterone levels before 10 AM.
- Normal ranges for testosterone vary among laboratories and assays. The Endocrine Society and Center for Disease Control recommends a lower limit of normal testosterone of 264ng/dL for total serum testosterone. The American Urological Association recommends a lower limit of normal total serum testosterone of less than 300ng/dL.
- TRT is contraindicated in men with known or suspected prostate or breast cancer.
- In 2015, the FDA concluded that there is a possible increased cardiovascular risk associated with testosterone use. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not. Labeling changes were required to outline this potential risk.
- The FDA requires manufacturer labeling to reflect the appropriate use of TRT, specifically as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism.
- In 2018, both the Endocrine Society and American Urological Association concluded that the evidence is inconclusive with regards to TRT and concerns for increased cardiovascular risk in hypogonadal men.

Estrogen replacement therapy (ERT)

- Used by biological females typically for the treatment of symptoms of menopause

- Also used for gender-affirming care in biological males
- ERT is available in several different formulations, including estradiol tablets, transdermal patches, injectable, and vaginal applications.
- There are no FDA approved estrogen formulations for pellet insertion; these products are often compounded

REFERENCE/RESOURCES:

1. Relevant package inserts
2. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. Available at http://www.fda.gov/drugs/drugsafety/ucm436259.htm (Accessed March 10, 2023)
3. The International Society for the Study of the Aging Male (ISSAM). Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*. 2015;18(1):5–15.
4. Morales A, Bebb RA, Manjoo P et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. *CMAJ*. 2015;187(18):1369-1377.
5. Shalender Bhasin, Juan P Brito, et al, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229
6. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, et al. Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. J Clin Endocrinol Metab. 2017;102(4):1161-73.
7. American Urological Association. Guidelines on Evaluation and Management of Testosterone Deficiency. Available at https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline (Accessed February 22, 2024).
8. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD): Treatment of Males with Low Testosterone (L36539). Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36569&ver=18&keyword=testosterone&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1 (Accessed March 10, 2023).

9. Centers for Medicare & Medicaid Services (CMS). Billing and Coding: Testopel Coverage (A55057). Available at https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=55057&ver=8&keyword=testosterone&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1 (Accessed March 10, 2023).

Table 1: Medications covered by this policy

Brand Name	Benefit
Aveed® testosterone vial	Medical
Testopel® pellet	Medical
Compounded estradiol and/or testosterone for use in pellet implantation	N/A – not coverable by Medicare

Appendix A: Available testosterone replacement therapies

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
Androgel®				
1%	5 g (4 pumps) applied topically once daily	10 g (8 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered pumps per package)	Applied to right and left upper arms /shoulders and/or right/left abdomen
1.62%	Initial: 40.5 mg (2 pumps) applied topically once daily	81 mg (4 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered pumps per package)	
Androderm® 2 mg/day & 4 mg/day	Apply topically once daily	1 patch per application	• 2 mg: 60 patches • 4 mg: 30 patches	Applied to the back, abdomen, upper arms, or thighs
Aveed®	3 mL by deep gluteal injection every 10 weeks	Same dose as standard	• 750/3 mL solution	Gluteal muscle
Axiron®	Initial: 60 mg (1 pump actuation to	120 mg (2 pumps actuations to each axilla)	• 110 mL (60 metered pumps per package)	Applied to the axilla only.

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
	each axilla) applied topically once daily			
Fortesta®	40 mg (4 pumps) applied topically once daily	70 mg (7 pumps)	• 60 g canister (120 metered pumps per package)	Applied to front and inner thighs only.
Vogelxo®	50 mg (1 tube or packet or 4 pumps) once daily	100 mg (2 tubes or packets or 8 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered pumps per package)	Applied to the shoulders and/or upper arms only.
Testim®	5 g (1 tube) applied topically once daily	10 g (2 tubes)	• #30 – 5 g tubes	Applied to the shoulders and/or upper arms only.
Jatenzo®	237 mg orally twice daily	396 mg twice daily	• Capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units per bottle.	Oral
Kyzatrex® Note: this product is only available direct from the manufacturer ("cash" pay) and cannot be billed through insurance	Recommended starting dose of 200 mg twice daily. Minimum recommended dose is 100 mg once daily.	400 mg twice daily	100 mg, 150 mg, and 200 mg capsules	Oral
Natesto™	1 actuation per nostril (5.5.mg per actuation) INTRANASALLY 3 times a day 6 to 8 hours apart for total daily dose of 33 mg	33 mg/ day – no dose adjustments are recommended. If testosterone levels remain below 300 ng/dL, treatment should be discontinued	Metered dose pump, containing 60 actuations (10day supply)	Nasal
Xyosted®	Initial: 75mg (1 autoinjector) subcut once weekly, titrate to trough concentration		Autoinjector (carton containing 4 autoinjectors) available as 50mg/0.5ml;	Administer subcutaneously in the abdominal region

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
	between 350 ng/dL and 650 ng/dL		75mg/0.5ml; or 100mg/0.5ml injectors	
Testopel®	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.	The suggested dosage for androgens varies depending on the age, and diagnosis of the individual patient. 150mg to 450mg subcutaneously every 3 to 6 months	75 mg testosterone pellets	Implanted subcutaneously in hip area or another fatty area
Compounded testosterone (not FDA approved)	Not determined – not FDA approved	Not determined – not FDA approved	Compounded for implantation	Implanted subcutaneously

Appendix 2. Available ERT products

Route of Administration	FDA-Approved Products
Oral	Estradiol tablets (Estrace®) Menest® (esterified estrogens) tablets Premarin® (conjugated estrogens) tablets
Injectable	Estradiol valerate (Delestrogen®) Estradiol cypionate
Implant insertion	Compounded estradiol for pellet insertion (not FDA approved)
Transdermal	Estradiol gel (Divigel®) Estradiol patch (Dotti®, Climara®, Vivelle-DOT® Estradiol cream (Estrace®)
Vaginal	Estradiol (Vagifem®) vaginal tablet Estradiol acetate (Femring®) vaginal ring Premarin® (conjugated estrogens) cream with applicator
Combination Products	Premphase®/Prempro® (conjugated estrogens/medroxyprogesterone) Esterified estrogens/methyltestosterone tablets

BILLING GUIDELINES AND CODING

Per Coding Policy 22.0 HCPCS S-Codes and H-Codes, S-codes are not accepted as billable codes; testosterone pellet (Testopel®) must be billed with the unclassified code.

Testopel® is limited to a maximum of six pellets per insertion. Medicare may only cover the number of pellets actually implanted in the patient (maximum of six pellets); wastage is not covered. Use of additional pellets may be paid on appeal if the documentation supports medical necessity as determined by the FDA approved drug label and the service complies with all Medicare requirements as indicated above.

INJECTABLE MEDICATIONS & ADMINISTRATION:	
DRUG CODE(S)	**Description**
J1071	Injection, testosterone cypionate, 1 mg
J3121	Injection, testosterone enanthate, 1 mg
J3145	Injection, testosterone undecanoate, 1 mg
96372	Ther/proph/diag inj sc/im
HORMONE PELLET & ADMINISTRATION	
DRUG CODE(S)	**Description**
J3490	Unclassified drugs (Testopel®)
11980*	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
**11980 may be covered when billed with J3490 for Testopel® for which there is an approved prior authorization on file. 11980 is not covered when billed separately and without J3490 for Testopel®*	
EXCLUSIONS	
J7999	Compounded drug, not otherwise classified
S0189	Testosterone pellet, 75 mg