Testosterone Agents – Topical/Buccal/Nasal/oral

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Testosterone Agents drug policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines.

FDA Approved Indications
Topical, buccal, nasal, implant, oral, and injectable testosterone products are indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, myotonic dystrophy, anorchia, testicular trauma or torsion, orchitis, testicular irradiation/damage, orchidectomy, Klinefelter Syndrome, chemotherapy, HIV infection, or end-stage renal disease. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

Secondary hypogonadism (i.e. hypogonadotropic hypogonadism) (congenital or acquired) - gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Limitations of Use
Safety and efficacy of topical, buccal, nasal, implant, oral, and injectable testosterone products in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.

Safety and efficacy of topical, buccal, nasal, implant, oral and injectable testosterone products in males less than 18 years old have not been established.
Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure.

**Compendial Uses**
Gender Dysphoria in Female-to-Male transgender

**POLICY**

**Criteria for Initial Approval**

A. Oral methyltestosterone tablets and capsules will be considered **medically necessary** when the following criteria are met for the requested indication:

1. **Primary or hypogonadotropic hypogonadism** [Note: Safety and efficacy of testosterone products in members with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.]
   - The member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation
   - Before the start of testosterone therapy, the member has at least two confirmed low testosterone levels according to current practice guidelines or your standard male lab reference values

   **Approval** will be for **36 months**.

2. **Breast cancer**
   - The member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation; AND the requested drug is being prescribed for one of the following:
     - Inoperable metastatic breast cancer in a member who is 1 to 5 years postmenopausal AND the patient had an incomplete response to other therapy for metastatic breast cancer; OR
     - Premenopausal member with breast cancer who has benefited from oophorectomy and is considered to have a hormone-responsive tumor

   **Approval** will be for **36 months**.

3. **Delayed puberty**
   - The drug is being prescribed for delayed puberty AND the member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation

   **Approval** will be for **36 months**.

B. All other testosterone products will be considered **medically necessary** when the following criteria are met for the requested indication:

1. **Primary hypogonadism**
   - Member has signs and symptoms of testosterone deficiency (see Appendix A)
   - Prior to initiating therapy, member has two confirmed low **total** testosterone levels drawn on separate days, during the morning, and in a fasted state UNLESS the member has anorchia or has undergone bilateral orchidectomy
   - Member does not have risk factors that are a contraindication to therapy (see Appendix B)
2. Secondary hypogonadism
   - Member has one of the following: congenital hypogonadotropic hypogonadism (also referred to as idiopathic hypogonadotropic hypogonadism), LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation
   - Functional causes that may be managed without testosterone treatment have been assessed (see Appendix C for examples)
   - Member has signs and symptoms of testosterone deficiency (see Appendix A)
   - Prior to initiating therapy, member has two confirmed low total testosterone levels drawn on separate days, during the morning, and in a fasted state
   - Member does not have risk factors that are a contraindication to therapy (see Appendix B)

   [Note: Safety and efficacy of testosterone products in members with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.]

3. Gender dysphoria
   - The requested drug is being prescribed for female-to-male gender reassignment
   - The member is 14 years of age or older and able to make an informed, mature decision to engage in therapy

   Approval will be for 12 months.

C. All Testosterone products are considered not medically necessary for members who do not meet the criteria set forth above.

Continuation Criteria
A. Continuation of therapy of oral methyltestosterone tablets and capsules may be considered medically necessary when the following criteria are met:
   - Criteria for Initial Approval has been met
   - Before the patient started testosterone therapy, the patient had a confirmed low testosterone level according to current practice guidelines or your standard male lab reference values

   Approval will be for 36 months.

B. Continuation of therapy of other testosterone products may be considered medically necessary when the following criteria are met:
   - Signs and symptoms have responded to treatment
   - Testosterone levels have been drawn within the past 12 months and are in the mid-normal range
   - Member has been assessed for adverse effects within the past 12 months and the member has not developed an adverse effect such as an elevated hematocrit or a prostatic abnormality that would require a discontinuation of testosterone therapy

   Approval will be for 12 months.

Dosing and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits
Jatenzo 158mg and 237mg capsules – 60 capsules/30 days
Jatenzo 198mg capsules – 120 capsules/30 days
APPENDICES

Appendix A

<table>
<thead>
<tr>
<th>Specific signs and symptoms</th>
<th>Suggestive signs and symptoms</th>
<th>Nonspecific signs and symptoms associated with testosterone deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete or delayed sexual development</td>
<td>Reduced sexual desire (libido) and activity</td>
<td>Decreased energy, motivations, initiative, and self-confidence</td>
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<tr>
<td>Loss of body (axillary and pubic) hair</td>
<td>Decreased spontaneous erections, erectile dysfunction</td>
<td>Feeling sad or blue, depressed mood, persistent low-grade depressive disorder</td>
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<tr>
<td>Very small testes (&lt;6 mL)</td>
<td>Breast discomfort, gynecomastia</td>
<td>Poor concentration and memory</td>
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<tr>
<td>Eunuchoidal body proportions</td>
<td>Sleep disturbance, increased sleepiness</td>
<td></td>
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<tr>
<td>Inability to father children, low sperm count</td>
<td>Mild unexplained anemia (normochromic, normocytic)</td>
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<tr>
<td>Height loss, low-trauma fracture, low BMD</td>
<td>Reduced muscle bulk and strength</td>
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<tr>
<td>Hot flashes, sweats</td>
<td>Increased body fat, body mass index</td>
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Appendix B

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<thead>
<tr>
<th>Very high risk of serious adverse outcomes</th>
<th>Moderate to high risk of adverse outcomes</th>
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<tbody>
<tr>
<td>Metastatic prostate cancer</td>
<td>Unevaluated prostate nodule or induration</td>
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<tr>
<td>Breast cancer</td>
<td>Unevaluated PSA&gt;4ng/mL (3ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with a first-degree relative with prostate cancer</td>
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<tr>
<td>Hematocrit &gt;48% (&gt;50% for men living at high altitude)</td>
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<tr>
<td>Severe LUTS associated with BPH as indicated by AUA/IPSS &gt;19</td>
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<tr>
<td>Poorly or un-controlled congestive heart failure</td>
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<tr>
<td>Desire for fertility in the near term</td>
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</table>

Abbreviations: AUA, America Urological Association; IPSS, International Prostate Symptom Score; BPH, Benign Prostatic Hyperplasia; PSA, prostate-specific antigen.

Appendix C

<table>
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<tr>
<th>Functional Causes of Secondary Hypogonadism</th>
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<tbody>
<tr>
<td>Hyperprolactinemia</td>
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<tr>
<td>Systemic illness</td>
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<tr>
<td>Nutritional deficiency/excessive exercise</td>
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<tr>
<td>Organ failure (liver, heart, lung)</td>
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CLINICAL RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Topical, buccal, and nasal testosterone products are indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: congenital or acquired primary hypogonadism

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(testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals), congenital or acquired hypogonadotropic hypogonadism (gonadotropin or luteinizing hormone-releasing hormone [LHRH] deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation). Safety and efficacy of topical, buccal, and nasal testosterone products in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.

A testosterone determination, in conjunction with a free testosterone or sex hormone-binding globulin level, is the threshold test in the evaluation of suspected male hypogonadism (serum total testosterone levels less than 300 ng/dL). Testosterone levels should be determined in the morning, and studies should be repeated in patients with subnormal levels. The normative ranges for total and free testosterone levels in healthy young men vary among laboratories and assays. In some laboratories, the lower limit of the normal range for total testosterone level in healthy young men is 280-300 ng/dL and for serum free testosterone level is 5–9 pg/mL. The clinicians should use the lower limit of normal range for healthy young men established in their laboratory. For initial and continuation of therapy, testosterone will be approved for patients with at least two confirmed low testosterone levels according to current practice guidelines or standard lab reference values.

Transgender persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will suppress endogenous hormone secretion determined by the person’s genetic/biologic sex and maintain sex hormone levels within the normal range for the person’s desired gender. The two major goals of hormonal therapy are to reduce endogenous hormone levels and, thereby, the secondary sex characteristics of the individual’s biological/genetic sex and to replace endogenous sex hormone levels with those of the reassigned sex. The Endocrine Society suggests that pubertal development of the desired opposite sex be initiated at about the age of 16 years, using a gradually increasing dose schedule of cross-sex steroids. However, the Endocrine Society Guidelines also state that identifying an age at which pubertal development is initiated is arbitrary, and the goal is to start the process at a time when the individual will be able to make informed, mature decisions to engage in the therapy. Therefore, individuals aged 14 years and older who are able to make an informed, mature decision to engage in therapy will be approved.

For female-to-male (FtM) transgender persons, regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism. Either parenteral or transdermal preparations can be used to achieve testosterone values in the normal male range (320-1000 ng/dL). The agent primarily used for endocrine treatment of FtM patients is testosterone. When determining the appropriate method of testosterone delivery, many considerations should be considered. The most well-described formulation of testosterone therapy used to treat FtM patients is intramuscular injection of testosterone esters (cypionate or enanthate). Because intramuscular testosterone cypionate or enanthate is often administered every 2-4 weeks, some patients may notice a cyclic variation in effects as well as more time outside the normal physiologic levels. Transdermal testosterone has been shown to provide less variation in serum testosterone levels compared with injectable preparations. Testosterone administered transdermally more closely mimics physiologic testosterone levels. However, transdermal preparations achieve low-normal ranges of testosterone levels in hypogonadal men, which may translate to a lessened change in physical appearance and virilization in the FtM patient.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Code(s), if applicable
REFERENCES

• Androgel 1% [package insert]. North Chicago, IL: Abbvie Inc; December 2018.
• Androgel 1.62% [package insert]. North Chicago, IL: Abbvie Inc; December 2018.
• Axiron [package insert]. Indianapolis, IN: Lilly USA, LLC; July 2018.

POLICY HISTORY

Policy #: 05.01.45
Policy Creation: September 2012
Reviewed: April 2019
Revised: April 2019
Current Effective Date: June 13, 2019