PRIOR AUTHORIZATION CRITERIA

DRUG CLASS **TESTOSTERONE PRODUCTS**

BRAND NAME*
(generic)

ANDRODERM
(testosterone transdermal patch)

ANDROGEL
(testosterone topical gel)

DELATESTRYL
(testosterone enanthate injection)

DEPO-TESTOSTERONE
(testosterone cypionate injection)

FORTESTA
(testosterone topical gel)

JATENZO
(testosterone undecanoate oral)

NATESTO
(testosterone nasal gel)

STRIANT
(testosterone mucoadhesive buccal system)

TESTIM
(testosterone topical gel)

TESTOPEL
(testosterone propionate implant pellets)

(testosterone topical solution)

VOGELXO
(testosterone topical gel)

XYOSTED
(testosterone enanthate)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization ***Ref # 1210-A***

** Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA-APPROVED INDICATIONS

Androderm, Androgel, Fortesta, Natesto, Striant, Testim, testosterone topical solution, Vogelxo

Topical, buccal, nasal, implant, 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 conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

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, 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, 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.

Delatestryl

Males

Delatestryl (Testosterone Enanthate Injection) is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.

Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. (Appropriate adrenal cortical and thyroid hormone replacement therapy are still necessary, however, and are actually of primary importance).

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Safety and efficacy of Delatestryl in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

Delayed puberty - Delatestryl (Testosterone Enanthate Injection) may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers.

Females

Metastatic Mammary Cancer - Delatestryl (Testosterone Enanthate Injection) may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or anti-estrogen therapy. This treatment has also been used in pre-menopausal women with breast cancer who have benefited from oophorectomy and are considered to a have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.

Depo-Testosterone
Depo-Testosterone Injection is indicated for replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone.
Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome; or orchiectomy.
Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropic or LHRH deficiency, or pituitary- hypothalamic injury from tumors, trauma or radiation.
Safety and efficacy of Depo-Testosterone (testosterone cypionate) in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

Jatenzo
Jatenzo is an androgen indicated for testosterone 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 conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
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 Jatenzo in males less than 18 years old have not been established.

Testopel
Males
Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.
Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome; or orchiectomy.
Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropic LHRH deficiency, or pituitary - hypothalamic injury from tumors, trauma or radiation.
If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sex characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.
Safety and efficacy of Testopel (testosterone pellets) in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be taken every 6 months to assess the effect of treatment on epiphyseal centers.

Xyosted
Xyosted (testosterone enanthate) injection is an androgen indicated for testosterone 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, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- 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 low or normal range.

Limitations of Use

- Safety and efficacy of Xyosted in males less than 18 years of age have not been established.

Compendial Uses

Gender Dysphoria[14-15, 18-21]

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The requested drug is being prescribed for primary or hypogonadotropic hypogonadism [Note: Safety and efficacy of testosterone products in patients with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.]
  AND
  - Before the start of testosterone therapy, the patient has at least two confirmed low morning testosterone levels according to current practice guidelines or your standard lab reference values **OR**
  - For continuation of testosterone therapy: before the patient started testosterone therapy, the patient had a confirmed low morning testosterone level according to current practice guidelines or your standard lab reference values

OR

- The requested drug is being prescribed for gender dysphoria in a patient who is able to make an informed decision to engage in hormone therapy

OR

- Testosterone enanthate injection (generic Delatestryl) is being prescribed for inoperable metastatic breast cancer in a patient who is 1 to 5 years postmenopausal AND the patient had an incomplete response to other therapy for metastatic breast cancer

OR

- Testosterone enanthate injection (generic Delatestryl) is being prescribed for a premenopausal patient with breast cancer who has benefited from oophorectomy and is considered to a have a hormone-responsive tumor

OR

- Testosterone enanthate injection (generic Delatestryl) or testosterone propionate implant pellets (Testopel) is being prescribed for delayed puberty

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, 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: congenital or acquired primary hypogonadism (testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or 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, nasal, implant, and injectable testosterone products in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.[1-16]

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 [nanograms per deciliter]). Testosterone levels should be determined in the morning, and studies should be repeated in patients with subnormal levels.[17] 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 (picograms per milliliter). Clinicians should use the lower limit of normal range for healthy young men established in their laboratory.[17,18] For initial therapy, testosterone will be approved for patients with at least two confirmed low morning testosterone levels according to current practice guidelines or standard lab reference values. If the patient is already on testosterone therapy and did not get a repeat testosterone level before starting therapy, it would be inappropriate for the patient to stop treatment to get

a repeat testosterone level. For continuation of therapy, one low morning testosterone level is required before the patient started testosterone therapy.

Testopel and Delatestryl may also be used to stimulate puberty in carefully selected males with clearly delayed puberty. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support.[5,12,15,16]

Delatestryl may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or anti-estrogen therapy.[1,15,16] Since testosterone is not a first-line drug for breast cancer, the patient must have had an incomplete response to other breast cancer therapy before using testosterone.

Delatestryl has also been used in pre-menopausal women with breast cancer who have benefited from oophorectomy and are considered to a have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.[5,15,16]

Injectable, oral, pellet, and transdermal testosterone formulations have a compendial use for gender dysphoria in transgender patients who were assigned female sex at birth.[19-21]

Transgender persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will suppress endogenous hormone secretion 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 birth-assigned gender and to replace endogenous sex hormone levels with those of the affirmed gender. The Endocrine Society suggests that pubertal development of the affirmed gender be initiated at about the age of 16 years, using a gradually increasing dose schedule of gender-affirming hormones. However, the Endocrine Society Guidelines also state that identifying an age at which pubertal development is initiated can be difficult and may depend on several factors (such as the age when pubertal suppression was begun, medications used to initiate pubertal suppression, relative risks of prolonged pubertal suppression, and the level of severity of the patient's distress due to gender dysphoria), 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 treatment. Some patients may advance to Tanner stage 2 of pubertal development at an early age (such as 9 or 10) and using pubertal suppression therapy for 6 or 7 years may be deemed inappropriate. Medical professionals involved in the patient's care should be involved in assessing whether the patient is ready to make the decision to begin hormone therapy and pubertal development.[19] Therefore, individuals who are able to make an informed decision to engage in hormone therapy will be approved.

For transgender male persons, regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism. Testosterone generally can be given orally, transdermally, or parenterally (IM) to achieve testosterone values in the normal male range (320-1000 ng/dL).[18,21] The agent primarily used for endocrine treatment of transgender male or transmasculine patients is testosterone. When determining the appropriate method of testosterone delivery, many considerations should be taken into account. The most well-described formulation of testosterone therapy used to treat transgender male patients is injectable testosterone esters (cypionate or enanthate).[20] 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.[21] Due to this cyclic variation, other preparations such as transdermal testosterone, oral testosterone, weekly subcutaneous testosterone enanthate injection or subcutaneous testosterone implant pellets may be considered. Transdermal testosterone has been shown to provide less variation in serum testosterone levels compared with injectable preparations and 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 transgender male patient.[20] Oral testosterone undecanoate formulations available outside the United States result in lower serum testosterone levels than nonoral preparations.[21] However, studies for Jatenzo indicate that it achieves normal serum testosterone levels in hypogonadal patients, indicating that normal levels can be achieved for transgender patients.

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Written by:	UM Development (CF/JH)
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Reviewed:	Medical Affairs: (DNC) 10/2014, 05/2015; (LCB) 11/2015; (SD) 02/2017; (AN) 02/2018; (ME) 10/2018, (GAD) 05/2019; (ME) 07/2019; (CHART) 02/27/20 External Review: 06/2016, 06/2017, 06/2018, 12/2018, 06/2019, 06/2020

CRITERIA FOR APPROVAL

1	Is the requested drug being prescribed for primary or hypogonadotropic hypogonadism? [Note: Safety and efficacy of testosterone products in patients with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.] [If no, then skip to question 5.]	Yes	No
2	Is this request for a continuation of testosterone therapy? [If no, then skip to question 4.]	Yes	No

3	Before the patient started testosterone therapy, did the patient have a confirmed low morning testosterone level according to current practice guidelines or your standard lab reference values? [No further questions.]	Yes	No
4	Does the patient have at least two confirmed low morning testosterone levels according to current practice guidelines or your standard lab reference values? [No further questions.]	Yes	No
5	Is the requested drug being prescribed for gender dysphoria in a patient who is able to make an informed decision to engage in hormone therapy? [If yes, then no further questions.]	Yes	No
6	Is this a request for testosterone propionate implant pellets (Testopel)? [If yes, then skip to question 10.]	Yes	No
7	Is this a request for testosterone enanthate injection (generic Delatestryl)? [If no, then no further questions.]	Yes	No
8	Is the requested drug being prescribed for a pre-menopausal patient with breast cancer who has benefited from oophorectomy and is considered to have a hormone-responsive tumor? [If yes, then no further questions.]	Yes	No
9	Is the requested drug being prescribed for inoperable metastatic breast cancer in a patient who is 1 to 5 years post menopausal AND has the patient had an incomplete response to other therapy for metastatic breast cancer? [If yes, then no further questions.]	Yes	No
10	Is the requested drug being prescribed for delayed puberty?	Yes	No

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Go to 5	
2.	Go to 3	Go to 4	
3.	Approve, 36 months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have had a test in the morning that showed low testosterone levels before you started testosterone therapy. Your request has been denied based on the information we have. [Short Description: No confirmation of diagnosis (tests, labs, etc.)]
4.	Approve, 36 Months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have had two tests in the morning that showed low testosterone levels. Your request has been denied based on the information we have. [Short Description: No confirmation of diagnosis (tests, labs, etc.)]
5.	Approve, 36 Months	Go to 6	
6.	Go to 10	Go to 7	
7.	Go to 8	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet one of these conditions: - You have primary or hypogonadotropic hypogonadism - You have gender dysphoria and you can make an informed decision to use this drug

			Your request has been denied based on the information we have. [Short Description: No approvable diagnosis (all drugs except Delatestryl and Testopel)]
8.	Approve, 36 Months	Go to 9	
9.	Approve, 36 Months	Go to 10	
10.	Approve, 36 Months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet one of these conditions: - You have primary or hypogonadotropic hypogonadism - You have gender dysphoria and you can make an informed decision to use this drug - You have delayed puberty - For testosterone enanthate injection (generic Delatestryl), you are a postmenopausal patient with metastatic breast cancer, surgery is not possible, and other drugs for your cancer did not work for you - For testosterone enanthate injection (generic Delatestryl), you are a premenopausal patient with breast cancer, have a hormone-responsive tumor, and had your ovaries removed Your request has been denied based on the information we have. [Short Description: No approvable diagnosis (Delatestryl and Testopel)]