Topical Androgens Step Therapy and Quantity Limit Criteria Program Summary

For BCBSAL, the preferred agents will include Androgel and Androderm. All others will be non-preferred and will be targets of the step therapy program. Quantity limits do apply.

Compounded testosterone products containing ingredients that are not FDA approved, including but not limited to bulk powders/chemicals/products and compound kits, do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered investigational. These compounded products are not included in this policy and are not covered.

OBJECTIVE
The intent of the Topical Androgens Step Therapy (ST) program is to encourage the use of the more cost-effective, preferred agent(s), when possible, before other nonpreferred topical androgen products. This step therapy program applies to males only; topical androgens will not be approved for use in females. Nonpreferred topical androgen products will be evaluated if the prescriber indicates a history of a trial of, documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred topical androgen(s). The program allows continuation of therapy when there is documentation that the patient is receiving the requested agent. Requests for nonpreferred topical androgens will be reviewed when patient-specific documentation has been provided.

Topical Androgen Products
Preferred Agents
Androderm® (testosterone transdermal system)
AndroGel® (testosterone gel)[b]

TARGET DRUGS
Non-Preferred Agents
Axiron® (testosterone solution)
Bio-T-Gel™ (testosterone gel)[a]
Fortesta™ (testosterone gel)
Natesto™ (testosterone nasal gel)
Striant® (testosterone buccal system)
Testim® (testosterone gel)
Testosterone (testosterone gel)
Vogelxo™ (testosterone gel)

a - FDA approved but not yet marketed; will be added to program when available
b - generic available and a stand alone agent; neither a preferred or non-preferred agent

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Axiron, Fortesta, Natesto, Striant, Testim, Testosterone or Vogelxo will be approved when BOTH of the following are met:

1. The patient is male
   AND
2. ONE of the following:

1. The patient's medication history indicates use of a preferred topical androgen in the past 90 days **OR**
2. There is documentation that the patient is currently using the requested agent **OR**
3. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed **OR**
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred topical androgen

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit document.

FDA APPROVED INDICATIONS AND DOSAGE[1-9,25,29,31]

Agent	Indications	Dosing and Administration
Androderm® (testosterone transdermal system) 2 mg/day, 4 mg/day transdermal system	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. -Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.	Hypogonadism <u>2 mg/day and 4 mg/day system</u> -Recommended starting dose is one 4 mg/day system (not two 2 mg/day systems) applied nightly for 24 hours. -Dose may be decreased to 2 mg (i.e., one 2 mg/day system) or increased to 6 mg (i.e., one 4 mg/day and one 2 mg/day system) <u>Switching from 2.5 mg/day, 5 mg/day, and 7.5 mg/day to 2 mg/day, 4 mg/day and 6 mg/day dosage</u> -Patients using 2.5 mg daily may be switched to 2 mg/day systems at the next scheduled dose -Patients using 5 mg daily may be switched to 4 mg/day systems at next scheduled dose -Patients using 7.5 mg daily may be switched to 6 mg (2 mg/day and 4 mg/day systems) at the next scheduled dose
AndroGel® (testosterone gel) 1% gel: 25 mg/2.5 gm packet[b] 50 mg/5 gm packet[b] 75 gm pump (12.5 mg testosterone /actuation; 60 actuations/pump[b]) 1.62% gel: 75 gm pump (20.25 mg testosterone /actuation; 60 actuations/pump) 20.25 mg/1.25gm and 40.5 mg/2.5 gm packets		<u>1% gel</u>: -Initial: 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet) once daily in the morning. -Dose may be increased to 75 mg and 100 mg daily based on measured serum testosterone levels. -If serum testosterone level exceeds normal range at 50 mg dose, therapy should be discontinued <u>1.62% gel</u>: -40.5 mg of testosterone (2 pump actuations or one 40.5 mg packet) applied topically once daily in the morning. -Dose may be adjusted between a minimum of 20.25 mg testosterone (1 pump actuation or 1 packet) or maximum 81 mg testosterone (4 pump actuations or 2 40.5 mg packets) based on measured serum testosterone levels.
Agent	**Indications**	**Dosing and Administration**
Axiron® (testosterone solution) 30 mg/1.5 mL, 90 mL pump		-Initial: 60 mg testosterone (2 pump actuations) applied once daily. -Dose of testosterone may be decreased to 30 mg (1 pump actuation) or increased to 90 mg (3 pump actuations) or 120 mg (4 pump actuations) based on the measured serum testosterone. -If serum testosterone concentration exceed 1050 ng/dL at 30 mg (1 pump

		actuation), therapy should be discontinued
Bio-T-Gel™ [a] (testosterone gel) 1% gel		1% gel: -Initial dose is 50 mg testosterone (5 gm gel) once daily in the morning. -Dose may be increased to 75 mg and 100 mg daily based on measured serum testosterone levels. -If serum testosterone level exceeds normal range at 50 mg dose, therapy should be discontinued.
Fortesta™/Testosterone Gel (testosterone gel) 2% gel, 60 gm pump		-Initial: 40 mg of testosterone (4 pump actuations) once daily in the morning. -Dose may be adjusted between a minimum of 10 mg of testosterone and a maximum of 70 mg of testosterone based on measured serum testosterone levels.
Natesto™ (testosterone nasal gel) 5.5 mg/actuation		Recommended dose of 11 mg (2 pump actuations, one per nostril), applied intranasally 3 times daily. If total testosterone concentrations consistently exceed 1040 ng/dL, therapy should be discontinued. If total testosterone concentrations are consistently below 300 ng/dL, an alternative treatment should be considered. Not recommended for use with nasally administered drugs other than sympathomimetic decongestants (e.g., oxymetazoline)
Striant® (testosterone buccal system) 30 mg buccal system		Usual dose is one buccal system (30 mg) to the gum region twice daily, morning and evening (about 12 hours apart).
Testim®/Testosterone Gel (testosterone gel) 1% gel, 5 gm tube		-Initial: 50 mg of testosterone (one tube) once daily in the morning. -Dose may be increased to 100 mg testosterone (two tubes) once daily based on measured serum testosterone.
Vogelxo™/Testosterone Gel (testosterone gel) 1% gel		-Initial dose is 50 mg testosterone (5 gm gel) once daily at the same time each day. -Dose may be increased to 100 mg daily based on measured serum testosterone levels. -The maximum recommended dose is 100 mg once daily.

a – FDA approved but not yet marketed; will be added to program when available
b – Generic available

FDA Labeled Contraindications[1-7,25,29]

Topical Androgen Products	
Agent	**Contraindications**
Androderm	1. Men with carcinoma of the breast or known or suspected

Androgel	carcinoma of the prostate 2. Women who are or may become pregnant, or who are breastfeeding
Axiron	
Bio-T-Gel	
Fortesta	
Natesto	
Striant	
Testim	
Testosterone	
Vogelxo	

CLINICAL RATIONALE

Efficacy

Therapeutically, testosterone is used in the management of hypogonadism (congenital or acquired). Testosterone is also the most effective exogenous androgen for the palliative treatment of carcinoma of the breast in postmenopausal women. Anabolic steroids possess the same pharmacologic functions as that of the androgens; however, have a much higher ratio of nitrogen-containing properties to increase muscle mass.[8]

The Endocrine Society Clinical Practice Guidelines (2010): Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes recommends the following:[9]
We suggest initiating testosterone therapy with any of the following regimens, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost.

- 75–100 mg of testosterone enanthate or cypionate administered intramuscularly (IM) weekly, or 150–200 mg administered every 2 weeks.
- One or two 5-mg nongenital, testosterone patches applied nightly over the skin of the back, thigh or upper arm, away from pressure areas.
- 5–10 g of a 1% testosterone gel applied daily over a covered area of nongenital skin (patients should wash hands after application).
- 30 mg of a bioadhesive buccal testosterone tablet applied to buccal mucosa every 12 hours.

The International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Academy of Andrology (EAA), and the American Society of Andrology (ASA) consensus statement on "Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism" includes the following recommendations:[10]

- Currently available intramuscular, subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician.

In an FDA safety communication [03-03-2015], FDA cautioned that the benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. Testosterone product manufacturers must clarify approved uses, and add information to labeling regarding possible increased risk of heart attacks and strokes in patients taking testosterone. Testosterone is FDA-approved 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. Examples of these disorders include failure of the testicles to produce testosterone due to genetic problems, or damage from chemotherapy or infection. FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in

men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established. [28]

Off Label Use
Androgens have been studied for use in AIDS/HIV-associated wasting syndrome. Clinical studies support the use of the following agents in men for AIDS/HIV-associated wasting syndrome: testosterone transdermal system,[13] testosterone enanthate,[14,15,18] and oxandrolone.[16,17] The use of topical testosterone to treat AIDS wasting in women is supported by several studies.[24,25] Oxandrolone was studied in both male and female pediatric patients.[17] Dosing for AIDS/HIV-associated wasting is as follows:

- testosterone transdermal system: Two 2.5 mg systems applied every 24 hours
- oxandrolone: Adults: 5 mg to 15 mg daily
  Adolescents and Children: 0.1 mg/kg/day for 12 weeks
- testosterone enanthate: 300 mg IM every 3 weeks for 6 months or 200 mg IM weekly

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease have a strong recommendation against the use of androgens as adjuvant to erythropoiesis-stimulating agent (ESA) treatment in anemia patients with chronic kidney disease.[19] The current guideline has serious safety concerns and states evidence for androgens' efficacy is low quality. Before the availability of epoetin therapy, androgens were used regularly in the treatment of anemia in dialysis patients.

The American Congress of Obstetricians and Gynecologists (ACOG) guidelines for vulvar skin disorders recommend a high potency topical steroid such as clobetasol propionate for treatment of lichen sclerosus. Topical testosterone has shown inconsistent results in trials.[20] The British Association of Dermatologists' guidelines state that "there appears to be no evidence base for the use of topical testosterone" for treatment of female anogenital lichen sclerosus.[23] Testosterone propionate has been used for decreased libido and vulva atrophy/dystrophy; such indications are not FDA approved. The Endocrine Society recommends against the generalized use of testosterone by women because the indications are inadequate and evidence of long-term studies is lacking.[21]

Safety
Androgens are associated with cardiomyopathy, increased low density lipoprotein (LDL), decreased high density lipoprotein (HDL), hepatotoxicity (including hepatic neoplasms), hypertrophy of the prostate and anabolic-androgenic steroids-induced hypogonadism.[11] Testosterone treatment in men aged 65 years and older who have limitations in mobility was associated with an increased risk for cardiovascular events, including myocardial infarction and hypertension, according to a study published by Basaria, et al.[12]

Since the possible development of an adverse event during treatment (especially elevated hematocrit or prostate carcinoma) requires rapid discontinuation of testosterone substitution, short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late onset hypogonadism.[10]

For additional clinical information see Prime Therapeutics Formulary Chapter 4.2: Androgens/Anabolic Steroids.

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ADDITIONAL INFORMATION

Definition of HIV Wasting Syndrome

The World Health Organization (WHO) clinical diagnosis of HIV wasting syndrome consists of "[u]nexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5; PLUS EITHER unexplained chronic diarrhea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas."[1]

Normal Testosterone Values

The Endocrine Society states "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 (9.8–10.4 nmol/liter). Similarly, in some reference laboratories, the lower limit of the normal range for serum free testosterone level, measured by the equilibrium dialysis method, is 5–9 pg/ml (0.17–0.31 nmol/liter). The clinicians should use the lower limit of normal range for healthy young men established in their laboratory."[2]

ADDITIONAL INFORMATION REFERENCES

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