



BlueCross BlueShield
of Alabama

Androgens and Anabolic Steroids Prior Authorization with Quantity Limit Through Preferred Topical Androgen Criteria Program Summary

This prior authorization program will apply only to the Oral and Topical Androgens and Anabolic Steroids.

Preferred topical agents is Androgel 1.62%.

This program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

Quantity limits only apply to the topical androgen agents.

OBJECTIVE

The intent of the Androgens and Anabolic Steroids Prior Authorization with Quantity Limit (PA) program is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. The PA criteria will approve these agents for the FDA approved indications and off label use that is medically necessary for certain indications (e.g. AIDS/HIV-associated wasting syndrome, Turner Syndrome). In addition, the program will encourage use of two preferred topical androgen agents (Androgel and Axiron) prior to a non-preferred topical androgen agent. Use of a non-preferred topical androgen agent will be evaluated if the prescriber indicates a history of a trial of or documented intolerance, FDA labeled contraindication, or hypersensitivity to two preferred topical androgen agents. Additionally, stand-alone topical agents will not require the use of preferred topical agents, nor be a requirement prior to use of non-preferred topical agents. The program will approve only one of these agents at a time. The program will approve topical androgens for doses within the FDA labeled dosage range. Determination of quantity limits takes into account the packaging of the agents. Quantity limits apply only to the topical androgens.

TARGET AGENTS

Topical Androgen Agents:

Preferred Agents

AndroGel® 1.62% (testosterone gel 1.62%)

Non-preferred Agents

Androderm® (testosterone transdermal system)

AndroGel® 1% (testosterone gel 1%)^b

Axiron® (testosterone solution)^b

Bio-T-Gel™ (testosterone gel)^e

Fortesta™ (testosterone gel)

Natesto™ (testosterone nasal gel)

Striant® (testosterone buccal system)

Testim® (testosterone gel)^b

Testosterone (testosterone gel)

Vogelxo™ (testosterone gel)

Stand-alone Agents

testosterone gel [generic AndroGel, generic Testim]

testosterone solution [generic Axiron]

Oral Androgen Agents:

Android® (methyltestosterone capsule)^d

Androxy® (fluoxymesterone tablet)

Methitest® (methyltestosterone tablet)

Testred® (methyltestosterone capsule)^d

Anabolic Steroid Agents:**Anadrol-50®** (oxymetholone)**danazol** [Danocrine®]^c**Oxandrin®** (oxandrolone)^d

a – Brand drug has been discontinued by the manufacturer but may still be available.

b – Generic available and included in prior authorization and quantity limit programs as a stand-alone product.

c – Brand drug no longer available in the U.S. Only generic available.

d – Generic available and included in prior authorization program only.

e – FDA approved but not yet marketed; will be added to program when available

PROGRAM QUANTITY LIMITS – TOPICAL ANDROGENS

Brand (generic)	GPI	Quantity Per Day Limit (or as noted)	Multisource Code
Topical Androgen Agents			
Androderm® (testosterone transdermal system)			
2 mg/day transdermal system	23100030008503	1 patch	M, N, O, or Y
4 mg/day transdermal system	23100030008510	1 patch	M, N, O, or Y
AndroGel® / Testosterone (testosterone gel)			
1% gel, 25 mg/2.5 gm packet ^b	23100030004025	2 packets	M, N, O, or Y
1% gel, 50 mg/5 gm packet ^b	23100030004030	2 packets	M, N, O, or Y
1% gel, 75 gm pump (1.25 gm/actuation; 60 actuations/pump)	23100030004040	10 gm/day (4 pumps/30 days)	M, N, O, or Y
1% gel, 2 x 75 gm pump (1.25 gm/actuation; 60 actuations/pump)	23100030004040	10 gm/day (4 pumps/30 days)	M, N, O, or Y
1.62% gel, 20.25 mg/1.25 gm packet	23100030004044	1 packet	M, N, O, or Y
1.62% gel, 40.5 mg/2.5 gm packet	23100030004047	2 packets	M, N, O, or Y
1.62% gel, 75 gm pump (1.25 gm/actuation; 60 actuations/pump)	23100030004050	5 gm/day (2 pumps/30 days)	M, N, O, or Y
Axiron® (testosterone solution)^b			
30 mg/1.5 mL, 90 mL pump	23100030002020	120 mg/day (2 pumps/30 days)	M, N, O, or Y
Bio-T-Gel™ (testosterone gel)			
1% gel, 25 mg/2.5 gm packet	GPI not available	2 packets	M, N, O, or Y
1% gel, 50 mg/5 gm packet	GPI not available	2 packets	M, N, O, or Y
Fortesta™ / Testosterone (testosterone gel)			
2% gel, 60 gm pump	23100030004070	80 mg/day ^c (2 pumps/30 days)	M, N, O, or Y
Natesto™ (testosterone nasal gel)			
5.5 mg/actuation, 7.32 gm pump (60 actuations/pump)	23100030004080	0.732 gram/day (3 pumps/30 days)	M, N, O, or Y
Striant® (testosterone buccal system)			
30 mg buccal system	23100030006320	2 systems	M, N, O, or Y
Testim® / Testosterone (testosterone gel)^b			
1% gel, 5 gm tube	23100030004030	2 tubes	M, N, O, or Y
Vogelxo™ / Testosterone (testosterone gel)			
1% gel, 50 mg/5 gm tube	23100030004030	2 tubes (300 gm/30 days)	M, N, O, or Y
1% gel, 50 mg/5 gm packet	23100030004030	2 packets (300 gm/30 days)	M, N, O, or Y
1% gel, 12.5 mg/actuation, 75 gm pump (carton of 2 pumps)	23100030004040	4 pumps/30 days (300 gm/30 days)	M, N, O, or Y

TARGET AGENTS – ORAL ANDROGENS AND ANABOLIC STEROIDS

Brand (generic)	GPI	Multisource Code
Oral Androgen Agents		
Android® (methyltestosterone)^b		
10 mg capsule	23100020000105	M, N, O, or Y
Androxy® (fluoxymesterone)		
10 mg tablet	23100010000315	M, N, O, or Y
Methitest® (methyltestosterone)		
10 mg tablet	23100020000310	M, N, O, or Y
Testred® (methyltestosterone)^b		
10 mg capsule	23100020000105	M, N, O, or Y
Anabolic Steroid Agents		
Anadrol-50® (oxymetholone)		
50 mg tablet	23200050000320	M, N, O, or Y
danazol [Danocrine®]^a		
50 mg capsule	23100005000105	M, N, O, or Y
100 mg capsule	23100005000110	M, N, O, or Y
200 mg capsule	23100005000115	M, N, O, or Y
Oxandrin® (oxandrolone)^b		
2.5 mg tablet	23200040000305	M, N, O, or Y
10 mg tablet	23200040000320	M, N, O, or Y

a - Brand drug no longer available; available as generic only.

b - Available as generic and included in the prior authorization program only.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Androderm, AndroGel, Axiron, Bio-T-Gel, Fortesta, Natesto, Striant, Testim, Testosterone, or Vogelxo will be approved when ALL of the following are met:

1. ONE of the following:
 - a. BOTH of the following:
 - i. The patient has AIDS/HIV-associated wasting syndrome, defined as unexplained involuntary weight loss (>10% baseline body weight) with obvious wasting OR body mass index <18.5 kg/m² AND all other causes of weight loss have been ruled out
AND
 - ii. ONE of the following:
 1. The patient is female
OR
 2. The prescriber has provided documentation that checking for testosterone levels is medically inappropriate for the patient’s gender
OR
 3. The patient has ONE of the following levels (documentation requirement to be determined by client):
 - a. The patient is not currently receiving testosterone replacement therapy AND has ONE of the following pretreatment levels:
 - i. Total serum testosterone level that is below the testing laboratory’s lower limit of the normal range or is less than 300 ng/dL
OR
 - ii. Free serum testosterone level that is below the testing laboratory’s lower limit of the normal range

- b. The patient is currently receiving testosterone replacement therapy AND the patient has ONE of the following current levels:
 - i. Total serum testosterone level that is within OR below the testing laboratory's lower limit of the normal range OR is less than 300 ng/dL
 - OR**
 - ii. Free serum testosterone level is within OR below the testing laboratory's normal range

OR

- b. ALL of the following:
 - i. The patient has primary or secondary (hypogonadotropic) hypogonadism
 - AND**
 - ii. Prior to testosterone replacement therapy, the patient had sign/symptom of hypogonadism
 - AND**
 - iii. ONE of the following levels (documentation requirement to be determined by client):
 - 1. The patient is not currently receiving testosterone replacement therapy AND has ONE of the following pretreatment levels:
 - a. Total serum testosterone level that is below the testing laboratory's lower limit of the normal range or is less than 300 ng/dL
 - OR**
 - b. Free serum testosterone level that is below the testing laboratory's lower limit of the normal range
 - OR**
 - 2. The patient is currently receiving testosterone replacement therapy AND the patient has ONE of the following current levels:
 - a. Total serum testosterone level that is within OR below the testing laboratory's lower limit of the normal range OR is less than 300 ng/dL
 - OR**
 - b. Free serum testosterone level is within OR below the testing laboratory's normal range

OR

- c. The patient has a diagnosis of gender identity disorder (GID) and ALL of the following:
 - i. The patient is an adult (18 years of age or older)
 - AND**
 - ii. The patient has received evaluation from TWO qualified mental health professionals who have independently assessed the patient and ALL of the following:
 - 1. At least one of the evaluating professionals must have a doctoral degree (PhD, MD, Ed.B, D.Sc, D.S.W. or Psy.D) and be capable of adequately evaluating co-morbid psychiatric conditions
 - AND**
 - 2. One evaluation should be from a person who has only had an evaluative role with the patient
 - AND**
 - 3. The evaluations document that the patient has demonstrated a knowledge and understanding of the expected outcomes of cross-sex hormone treatment, as well as the medical and social risks and benefits
 - AND**
 - iii. ONE of the following:

1. The patient does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment

OR

2. If the patient has significant medical or mental health issues present, they must be reasonably well controlled and noted in the medical documentation submitted

AND

- iv. For patients new to therapy, the patient has completed at least 12 continuous months of living in a congruent gender role with his/her gender identity (real life experience) prior to cross-sex hormone treatment (this should be noted in medical documentation submitted including start/end dates)

AND

2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

3. ONE of the following:

- a. The requested agent is a preferred topical androgen agent (Androgel 1.62%)

OR

- b. The requested agent is a stand-alone topical androgen agent

OR

- c. ONE of the following:

- i. The patient's medication history indicates use of a preferred topical androgen agent (Androgel 1.62%)

OR

- ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred topical androgen agent

AND

4. ONE of the following:

- a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)

OR

- b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent

OR

- c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

AND

5. ONE of the following:

- a. The quantity requested is within the set quantity limit

OR

- b. The quantity (dose) requested is within FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength

OR

- c. The quantity (dose) requested is greater than the maximum dose recommended in FDA labeling and prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Android, Androxy, Methitest, Testred will be approved when ALL of the following are met:

1. ONE of the following:

- a. ALL of the following:

- i. ONE of the following:

1. The patient has cryptorchidism

OR

2. BOTH of the following:
 - a. The patient has hypogonadism
AND
 - b. Prior to testosterone replacement therapy, the patient had sign/symptom of hypogonadism
- OR**
3. BOTH of the following:
 - a. ONE of the following:
 - i. The patient is male
OR
 - ii. The prescriber has provided documentation that the requested agent is medically appropriate for the patient's gender
 - AND**
 - b. The patient is an adolescent with delayed puberty
- AND**
- ii. ONE of the following:
 1. The patient is not currently receiving testosterone replacement therapy **AND** has ONE of the following pretreatment levels:
 - a. Total serum testosterone level that is below the testing laboratory's lower limit of the normal range or is less than 300 ng/dL
OR
 - b. Free serum testosterone level that is below the testing laboratory's lower limit of the normal range
 - OR**
 2. The patient is currently receiving testosterone replacement therapy **AND** the patient has ONE of the following current levels:
 - a. Total serum testosterone level that is within **OR** below the testing laboratory's lower limit of the normal range **OR** is less than 300 ng/dL
OR
 - b. Free serum testosterone level is within **OR** below the testing laboratory's normal range
- OR**
- b. The patient has metastatic/inoperable breast cancer
OR
- c. The patient has a diagnosis of gender identity disorder (GID) and ALL of the following:
 - i. The patient is an adult (18 years of age or older)
AND
 - ii. The patient has received evaluation from TWO qualified mental health professionals who have independently assessed the patient and ALL of the following:
 1. At least one of the evaluating professionals must have a doctoral degree (PhD, MD, Ed.B, D.Sc, D.S.W. or Psy.D) and be capable of adequately evaluating co-morbid psychiatric conditions
AND
 2. One evaluation should be from a person who has only had an evaluative role with the patient
AND
 3. The evaluations document that the patient has demonstrated a knowledge and understanding of the expected outcomes of cross-sex hormone treatment, as well as the medical and social risks and benefits

- iii. **AND**
 - ONE of the following:
 - 1. The patient does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment
 - OR**
 - 2. If the patient has significant medical or mental health issues present, they must be reasonably well controlled and noted in the medical documentation submitted
- iv. **AND**
 - For patients new to therapy, the patient has completed at least 12 continuous months of living in a congruent gender role with his/her gender identity (real life experience) prior to cross-sex hormone treatment (this should be noted in medical documentation submitted including start/end dates)

- AND**
- 2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
- AND**
- 3. ONE of the following:
 - a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)
 - OR**
 - b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent
 - OR**
 - c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 6 months (delayed puberty only)
12 months (all other indications)

Anadrol-50 will be approved when ALL of the following are met:

- 1. ONE of the following:
 - a. BOTH of the following:
 - i. The patient has ONE of the following diagnoses:
 - 1. Patient has anemia caused by deficient red cell production, including acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs
 - OR**
 - 2. Patient has anemia associated with chronic renal failure AND ONE of the following:
 - a. The patient's medication history indicates previous use of an erythropoiesis-stimulating agent
 - OR**
 - b. The patient has documented intolerance, FDA labeled contraindication or hypersensitivity to an erythropoiesis-stimulating agent
 - ii. The patient has a hematocrit (Hct) value <30%
 - OR**
 - b. The patient has a diagnosis of gender identity disorder (GID) and ALL of the following:
 - i. The patient is an adult (18 years of age or older)
 - AND**

- ii. The patient has received evaluation from TWO qualified mental health professionals who have independently assessed the patient and ALL of the following:
 - 1. At least one of the evaluating professionals must have a doctoral degree (PhD, MD, Ed.B, D.Sc, D.S.W. or Psy.D) and be capable of adequately evaluating co-morbid psychiatric conditions
AND
 - 2. One evaluation should be from a person who has only had an evaluative role with the patient
AND
 - 3. The evaluations document that the patient has demonstrated a knowledge and understanding of the expected outcomes of cross-sex hormone treatment, as well as the medical and social risks and benefits
AND
- iii. ONE of the following:
 - 1. The patient does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment
OR
 - 2. If the patient has significant medical or mental health issues present, they must be reasonably well controlled and noted in the medical documentation submitted
AND
- iv. For patients new to therapy, the patient has completed at least 12 continuous months of living in a congruent gender role with his/her gender identity (real life experience) prior to cross-sex hormone treatment (this should be noted in medical documentation submitted including start/end dates)

AND

- 2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND
- 3. One of the following:
 - a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)
OR
 - b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent
OR
 - c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Danazol will be approved when ALL of the following are met:

- 1. The patient has ONE of the following diagnoses:
 - a. Patient has fibrocystic breast disease
OR
 - b. Patient has hereditary angioedema
OR
 - c. Patient has endometriosis
OR
 - d. The patient has a diagnosis of gender identity disorder (GID) and ALL of the following:

- i. The patient is an adult (18 years of age or older)
AND
- ii. The patient has received evaluation from TWO qualified mental health professionals who have independently assessed the patient and ALL of the following:
 - 1. At least one of the evaluating professionals must have a doctoral degree (PhD, MD, Ed.B, D.Sc, D.S.W. or Psy.D) and be capable of adequately evaluating co-morbid psychiatric conditions
AND
 - 2. One evaluation should be from a person who has only had an evaluative role with the patient
AND
 - 3. The evaluations document that the patient has demonstrated a knowledge and understanding of the expected outcomes of cross-sex hormone treatment, as well as the medical and social risks and benefits
AND
- iii. ONE of the following:
 - 1. The patient does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment
OR
 - 2. If the patient has significant medical or mental health issues present, they must be reasonably well controlled and noted in the medical documentation submitted
AND
- iv. For patients new to therapy, the patient has completed at least 12 continuous months of living in a congruent gender role with his/her gender identity (real life experience) prior to cross-sex hormone treatment (this should be noted in medical documentation submitted including start/end dates)

AND

- 2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND
- 3. ONE of the following:
 - a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)
OR
 - b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent
OR
 - c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Oxandrin (oxandrolone) will be approved when ALL of the following are met:

- 1. The patient has ONE of the following diagnoses:
 - a. Patient has AIDS/HIV-associated wasting syndrome (defined as unexplained involuntary weight loss >10% baseline body weight with obvious wasting or body mass index <18.5 kg/m²) AND all other causes of weight loss have been ruled out
OR
 - b. BOTH of the following:

- i. ONE of the following:
 - 1. The patient is female**OR**
 - 2. The prescriber has provided documentation that the requested agent is medically appropriate for the patient's gender

AND

- ii. Patient is a child or adolescent with Turner syndrome AND is currently receiving growth hormone

OR

- c. Patient has weight loss following extensive surgery, chronic infections, or severe trauma

OR

- d. Patient has chronic pain from osteoporosis

OR

- e. Patient is on long-term administration of oral or injectable corticosteroids

OR

- f. The patient has a diagnosis of gender identity disorder (GID) and ALL of the following:

- i. The patient is an adult (18 years of age or older)

AND

- ii. The patient has received evaluation from TWO qualified mental health professionals who have independently assessed the patient and ALL of the following:

- 1. At least one of the evaluating professionals must have a doctoral degree (PhD, MD, Ed.B, D.Sc, D.S.W. or Psy.D) and be capable of adequately evaluating co-morbid psychiatric conditions

AND

- 2. One evaluation should be from a person who has only had an evaluative role with the patient

AND

- 3. The evaluations document that the patient has demonstrated a knowledge and understanding of the expected outcomes of cross-sex hormone treatment, as well as the medical and social risks and benefits

AND

- iii. ONE of the following:

- 1. The patient does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment

OR

- 2. If the patient has significant medical or mental health issues present, they must be reasonably well controlled and noted in the medical documentation submitted

AND

- iv. For patients new to therapy, the patient has completed at least 12 continuous months of living in a congruent gender role with his/her gender identity (real life experience) prior to cross-sex hormone treatment (this should be noted in medical documentation submitted including start/end dates)

AND

- 2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

AND

- 3. ONE of the following:

- a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)

OR

- b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent
- OR**
- c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE^{1-11,27,28,32,33,37-39,41,42,46,50}

Topical Androgen Agents		
Agent	Indication	Dosage and Administration
<p>Androderm® (testosterone transdermal system)</p> <p>2 mg/day, 4 mg/day transdermal system</p>	<p>For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:</p> <p>-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.</p> <p>-Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.</p>	<p>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)</p> <p><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 the 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</p>
<p>AndroGel® / Testosterone (testosterone gel)</p> <p>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)</p> <p>1.62% gel: 75 gm pump (20.25 mg testosterone/actuation; 60 actuations/pump) 20.25 mg/1.25gm packet 40.5 mg/2.5 gm packet</p>	<p>(LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.</p>	<p><u>1% gel:</u> -Initial dose is 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.</p> <p><u>1.62% gel:</u> -40.5 mg of testosterone (2 pump actuations or 1 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.</p>

Topical Androgen Agents		
Agent	Indication	Dosage and Administration
Axiron® (testosterone soln) ^b 30 mg/1.5 mL, 90 mL pump		-Initial dose is 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 exceeds 1050 ng/dL at 30 mg, therapy should be discontinued.
Fortesta™ / Testosterone (testosterone gel) 2% gel		-Initial dose is 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)		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 (testosterone gel) ^b 1% gel		-Initial dose is 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.

Topical Androgen Agents		
Agent	Indication	Dosage and Administration
Vogelxo™/Testosterone (testosterone gel) 1% gel	For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: -Primary hypogonadism -Hypogonadotropic hypogonadism (congenital or acquired)	<u>1% gel:</u> -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.
Bio-T-Gel™ (testosterone gel) 1% gel		<u>1% gel:</u> -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.

a – Brand drug no longer available; available as generic only.

b – Generic available.

c – Brand drug has been discontinued by the manufacturer but may still be available.

Oral Androgen and Anabolic Agents		
Agent	Indication	Dosage and Administration
Android® (methyltestosterone) 10 mg capsule ^b	<u>Males:</u> Androgen replacement therapy related to the following: -Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchidectomy -Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin or LHRH deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation -Delayed puberty in males <u>Females:</u> Palliative treatment of breast cancer in women	<u>Males:</u> -Androgen replacement therapy related to hypogonadism: 10 mg to 50 mg/day -Androgen replacement therapy related to cryptorchidism: 10 mg 3 times daily -Delayed puberty (adolescents only): 5 mg to 25 mg/day for a limited period, usually for 4 to 6 months <u>Females:</u> -50 mg once daily up to four times/day -If suitable response within 2-4 weeks, decrease to 25 mg two times daily
Methitest® (methyltestosterone) 10 mg tablet		
Testred® (methyltestosterone) 10 mg capsule ^b		
Androxy® (flouxymesterone) 10 mg tablet	<u>Males:</u> -Androgen replacement therapy in male hypogonadism -Treatment of delayed puberty in males <u>Females:</u> Inoperable breast cancer	<u>Males:</u> -Androgen replacement: 5 mg given 1 to 4 times daily, although higher initial doses (i.e. 10 mg/day) with subsequent dose adjustment are usually preferable -Delayed puberty (adults/adolescents): 2.5 mg - 10 mg daily for up to 4 to 6 months. Doses up to 20 mg daily have been used. <u>Females:</u> 10 mg - 40 mg per day in divided doses. Treatment should continue at least 2-3 months
Anadrol-50® (oxymetholone) 50 mg tablet	Treatment of anemias caused by deficient red cell production. Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs often respond	<u>Adults and children</u> -1 to 5 mg/kg body weight per day. -Usual effective dose is 1 to 2 mg/kg/day; higher doses may be required, dose should be individualized. -Response is not often immediate; minimum trial of 3 to 6 months should be given -Following remission, some patients may be maintained without the drugs; others may be maintained on an established lower daily dosage -A continued maintenance dose is usually necessary in patients with congenital aplastic anemia

Oral Androgen and Anabolic Agents		
Agent	Indication	Dosage and Administration
<p>danazol [Danocrine®]^a</p> <p>50 mg, 100 mg, 200 mg capsule</p>	<p>-Fibrocystic breast disease -Angioedema prophylaxis in patients with hereditary angioedema -Endometriosis amenable to hormone management</p>	<p>-Fibrocystic breast disease: 100 to 400 mg/day in 2 divided doses. Although symptoms may be relieved, and even eliminated in 3 months, up to 6 months of uninterrupted therapy may be required to eliminate nodularity.</p> <p>-Angioedema prophylaxis: Initial 200 mg two to three times daily. If a favorable response achieved, dose may be reduced by half at intervals of 1-3 months. If unfavorable response (attack of angioedema during treatment), dose may be increased by up to 200 mg/day. NOTE: If danazol therapy initiated during exacerbation of angioedema caused by trauma, stress or other causes, periodic attempts to reduce or discontinue therapy should be considered</p> <p>-Endometriosis: In moderate/severe disease or patients infertile due to endometriosis: starting dose of 800 mg given in two divided doses. Gradual downward titration to dose sufficient to maintain amenorrhea may be considered. In mild disease: starting dose of 200 mg to 400 mg given in two divided doses; adjust depending on patient response. Continue therapy for 3 to 6 months, may be extended to 9 months if necessary.</p>
<p>Oxandrin® (oxandrolone)^b</p> <p>2.5 mg, 10 mg tablet</p>	<p>-Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, severe trauma, and in some patients without definite pathophysiologic reasons who fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis</p>	<p><u>Adults</u> -Daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. -Desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. -A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated. <u>Children</u>: Total daily dosage is ≤ 0.1 mg/kg body weight or ≤ 0.045 mg per pound of body weight. This may be repeated intermittently as indicated <u>Geriatric</u>: 5 mg twice daily</p>

a – Brand drug no longer available; available as generic only.

b – Generic available.

c – Brand drug has been discontinued by the manufacturer but may still be available.

Injectable Androgen Agents		
Agent	Indication	Dosage and Administration
<p>Delatestryl® (testosterone enanthate)^{b,c}</p> <p>200 mg/mL</p>	<p><u>Males:</u> For replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:</p> <p>-Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy</p> <p>-Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. Prior to puberty, androgen replacement therapy needed during adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty</p> <p>-Delayed puberty</p> <p><u>Females:</u> Palliative treatment of breast cancer that is inoperable in women</p>	<p><u>Males:</u></p> <p>-Hypogonadism</p> <ul style="list-style-type: none"> • Adult males: 50 mg to 400 mg IM every 2 to 4 weeks • Children (initiation of pubertal growth): 40 mg to 50 mg/m² IM monthly until growth rate falls to prepubertal levels. <ul style="list-style-type: none"> ○ Terminal growth phase: 100 mg/m² IM monthly until growth ceases ○ Maintenance of virilization: 100 mg/m² IM twice monthly <p>-Delayed puberty: 50 mg to 200 mg IM every 2 to 4 weeks for a limited duration, for example, 4 to 6 months or 40 mg to 50 mg/m²/dose IM monthly for 6 months</p> <p><u>Females:</u></p> <p>-Palliation of inoperable breast cancer: 200 mg to 400 mg IM every 2 to 4 weeks</p>
<p>Depo-Testosterone® (testosterone cypionate)^b</p> <p>100 mg/mL, 200 mg/mL</p>	<p>For replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone:</p> <p>-Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.</p> <p>-Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.</p>	<p>-Hypogonadism: 50-400 mg every 4 weeks</p>

Injectable Androgen Agents		
Agent	Indication	Dosage and Administration
Testopel® (testosterone pellets) 75 mg	1. <u>Males:</u> -Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy -Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. -Delayed puberty	-Hypogonadism (adult males and children): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months <ul style="list-style-type: none"> • Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally <ul style="list-style-type: none"> ○ For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3–6 months -Delayed puberty (adolescents only): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months, although the lower end of the dosing range is typically sufficient <ul style="list-style-type: none"> • Treatment is usually only required for 4–6 months • Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3–6 months
Aveed™ (testosterone undecanoate) 250 mg/mL	-Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy -Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation	The recommended dose of Aveed is 3 mL (750 mg) injected intramuscularly, followed by 3 mL (750 mg) injected after 4 weeks, then 3 mL (750 mg) injected every 10 weeks thereafter.

a – Brand drug no longer available; available as generic only.

b – Generic available.

c – Brand drug has been discontinued by the manufacturer but may still be available.

CLINICAL RATIONALE

Efficacy

Androgen Deficiency Syndromes

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.¹¹

Testosterone replacement therapy should be initiated in symptomatic men with hypogonadism. Signs and symptoms include:¹²

- More specific:
 - Incomplete or delayed sexual development, eunuchoidism
 - Reduced sexual desire (libido) and activity
 - Decreased spontaneous erections
 - Breast discomfort, gynecomastia
 - Loss of body (axillary and pubic) hair, reduced shaving
 - Very small (especially <5 ml) or shrinking testes
 - Inability to father children, low or zero sperm count
 - Height loss, low trauma fracture, low bone mineral density
 - Hot flushes, sweats
- Less specific:
 - Decreased energy, motivation, initiative, and self-confidence
 - Feeling sad or blue, depressed mood, dysthymia
 - Poor concentration and memory
 - Sleep disturbance, increased sleepiness
 - Mild anemia (normochromic, normocytic, in the female range)
 - Reduced muscle bulk and strength
 - Increased body fat, body mass index
 - Diminished physical or work performance

The Endocrine Society Clinical Practice Guidelines (2010): Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes recommends the following:¹²

- Initiate 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.

Endocrine Society Guidelines also state that when hypogonadal men were treated with oral testosterone, there was no increase in functional mobility or muscle strength compared with placebo. The oral formulations (17- α -methyltestosterone) should not be used in treatment of androgen deficiency due to variable response rates and risk of liver toxicity.¹²

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:¹³

- 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.⁴⁵

Hereditary Angioedema (HAE)

A review (2015) states despite lack of large, randomized, placebo-controlled trials, the efficacy of attenuated androgens (e.g., danazol) in the long-term prophylaxis of type I and II HAE is well established and widely accepted. Advantages of androgen use include convenience of oral dosing and low medication cost relative to other HAE therapies. The minimum effective androgen dose that controls HAE attacks is recommended to reduce risk of short-term and long-term adverse effects. Androgen therapy may be effective for most patients with HAE; however, potential risks and adverse effects must be carefully considered and discussed with patients when considering options for long term HAE prophylaxis. In keeping with current HAE consensus guidelines, disease management programs should be tailored individually, taking into consideration patient priorities and preferences, preexisting comorbid medical conditions, and the risk benefit profiles of different treatment options.⁴⁹

A review on treatment of HAE (2014) suggests attenuated androgens and plasma-derived C1-inhibitor (C1-INH) concentrates are the recommended options for long term prophylaxis of HAE. Antifibrinolytic agents have also undergone controlled clinical trials against placebo, but the efficacy data for them is inferior. Danazol is the most commonly used androgen. An alternative for short-term prophylaxis is initiation of daily danazol 5 to 7 days before a procedure and 2 days after the procedure. Efficacy of androgens vs. C1-INH replacement has not been studied for preprocedural prophylaxis. Androgens may be used when the surgery-related risk is relatively low and when C1-INH concentrate is not available. Adverse events with short-term use of androgens are minimal. They are less expensive and easier to use although they are not suitable for pregnant and nursing females. Long-term treatment with androgens is associated with a wide range of potential, dose-dependent adverse effects. Risks may outweigh benefits if dose is more than equivalent of 200 mg of danazol daily.⁴⁴

The U.S. HAE Association Medical Advisory Board (2013) recommendations for patients with HAE due to C1-INH deficiency list danazol among treatment options for prophylaxis of HAE. The only other FDA approved agent is plasma derived C1-INH therapy; other options are used off label. It is the position of the board that these medications should not be used in patients who express a preference for an alternative therapy and that patients should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1-INH concentrate.⁴³

It is important to avoid anabolic androgens for long-term prophylaxis in patients age <16 or in pregnant or breastfeeding women. Anabolic androgens should also be avoided if not tolerated or there are troubling adverse effects. All patients receiving attenuated androgens need to be carefully followed-up for the potential of medication-related adverse effects.⁴³

Evidence based recommendations for the Therapeutic Management of Angioedema due to hereditary C1 inhibitor deficiency: Consensus Report of an International Working Group (2012) states the following: There was consensus that danazol can be considered for long term prophylaxis for patients who are >16 years of age and non-pregnant and non-lactating women (in those patients who can tolerate it and the dosage does not exceed 200 mg/day).³⁴

The World Allergy Organization guideline (2012) for the management of HAE also states danazol may be used for short term/pre-procedural prophylaxis when the surgery-related risk is relatively low and when C1-INH concentrate is not available. Advantages are ease of use, good tolerability for most, including children, and low cost. Disadvantages are perceived inferior efficacy to C1-INH concentrate (although evidence is lacking), use in case of elective surgery only, side effects and unsuitability for pregnant (except last trimester) or breastfeeding women.³⁵

Off Label Use

Androgens and anabolic steroids have been studied for use in AIDS/HIV-associated wasting syndrome and Turner syndrome. Clinical studies support the use of the following agents in men for AIDS/HIV-associated wasting syndrome: testosterone transdermal system¹⁷, testosterone enanthate^{18,19,22}, oxandrolone^{20,21}, and cypionate⁴⁸. The use of topical testosterone to treat AIDS wasting in women is supported by several studies.^{30,31} Oxandrolone was studied in both male and female pediatric patients.²¹ 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 Turner Syndrome Consensus Study Group, sponsored by the National Institutes of Health's National Institute of Child Health and Human Development, recommends oxandrolone for treatment of Turner syndrome, when used in conjunction with growth hormone (GH).¹⁶ Recommended dose of oxandrolone is 0.05 mg/kg/d or less in conjunction with growth hormone only. Therapy may be continued until a satisfactory height has been attained or until little growth potential remains (bone age \geq 14 yr and growth velocity <2 cm/yr).

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.²³ 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 DMD (Duchenne muscular dystrophy) Care Considerations Working Group guidelines recommend glucocorticoids as first-line treatment for Duchenne muscular dystrophy. Glucocorticoids are the only medication currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Oxandrolone is not considered necessary or appropriate, either with or without glucocorticoid therapy.²⁴

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.²⁵ 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

sclerosis.²⁹ 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.²⁶

The American Urology Association (AUA) recommends that phosphodiesterase type 5 inhibitors should be first-line therapy for erectile dysfunction. AUA also recommend that testosterone therapy is not indicated for the treatment of erectile dysfunction in patients with a normal serum testosterone level. Also, the role of testosterone therapy in men with sexual dysfunction with low, borderline normal, and normal testosterone levels is not well defined.⁴⁰

Safety

Androgens and anabolic steroids 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.¹⁴ 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.¹⁵ Anabolic steroids are mainly abused by males and athletes to increase muscle mass and improve athletic performance.

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.¹³

On September 17, 2014, the FDA Bone, Reproductive and Urologic Drugs Advisory Committee stated that the available studies informing the cardiovascular safety signal with testosterone therapy are limited in scope, quality, design, and size. Nonetheless, there was agreement amongst committee members that a weak signal of cardiovascular risk had emerged from results of cardiovascular-related adverse events with testosterone use. The committee agreed that additional studies on the risk of therapy are needed to assess cardiovascular and other risks associated with short term and long term use of testosterone for age-related hypogonadism.³⁶

Prescribing information (2015) for testosterone products contains the following warnings: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with the use of testosterone replacement therapy. Safety and efficacy in men with "age-related hypogonadism" have not been established. Safety and efficacy in males less than 18 years old have not been established.

A retrospective cohort study (2015) compared cardiovascular safety of testosterone injections, patches, and gels. Adult male initiators (N=431,687) of new dosage formulations of testosterone patches, gels, or injections following 180 days free of any testosterone use were followed for up to one year of use. Of the subjects followed, 36% used injection products, 9% used patch products, and 55% used gel products. Testosterone injections were associated with a greater risk of CV events, hospitalizations, and deaths vs. gels. Patches and gels had similar risk profiles. This study did not assess whether patients met criteria for use of testosterone and did not assess the safety of testosterone among users compared to non-users of the drug.⁴⁷

On October 25th, 2016, the FDA approved a class wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence

section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other Androgen, Anabolic Steroids (AAS). The new Warning will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse. In addition to the new Warning, all testosterone labeling has been revised to include information in the Abuse and Dependence section about adverse outcomes reported in association with abuse and dependence of testosterone/AAS, and information in the Warning and Precautions section advising prescribers of the importance of measuring serum testosterone concentration if abuse is suspected.⁵¹

REFERENCES

1. Androderm prescribing information. Actavis Pharma, Inc. October 2016.
2. AndroGel 1% prescribing information. AbbVie Inc. October 2016.
3. AndroGel 1.62% prescribing information. AbbVie Inc. October 2016.
4. Axiron prescribing information. Lilly USA. October 2016.
5. Fortesta prescribing information. Endo Pharma, Inc. October 2016.
6. Striant prescribing information. Actient Pharmaceuticals LLC. October 2016.
7. Testim prescribing information. Auxilium Pharma, Inc. October 2016.
8. Oxandrin prescribing information. Savient Pharma, Inc. June 2005.
9. Anadrol-50 prescribing information. Unimed Pharma, Inc. August 2004.
10. Delatestryl prescribing information. Endo Pharma, Inc. October 2016.
11. Clinical Pharmacology. <http://www.clinicalpharmacology-ip.com/default.aspx> Accessed on September 28, 2011.
12. Shalender B, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536-2559.
13. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. *Eur j Endocrinology* 2008;(159): 507-514.
14. Kanayama G, Hudson JI, Pope HG Jr. Illicit anabolic-androgenic steroid use. *Horm Behav.* 2010 Jun;58(1):111-21.
15. Basaria S, Coviello AD, Travison T, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-122.
16. Bondy CA, for the Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007;92:10-25.
17. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab.* 1998 Sep;83(9):3155-62.
18. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;129:18-26.
19. Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. *Ann Intern Med* 2000;133:348-355.
20. Berger JR, Pall L, Hall CD, et al. Oxandrolone in AIDS-wasting myopathy. *AIDS* 1996;10:1657-1662.
21. Fox-Wheeler S, Heller L, Salata CM, et al. Evaluation of the effects of oxandrolone on malnourished HIV-positive pediatric patients. *Pediatrics* 1999;104:E731-E737.
22. Coodley GO, Coodley MK. A trial of testosterone therapy for HIV-associated weight loss. *AIDS.* 1997 Sep;11(11):1347-52.
23. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis.* 2006 May; 47(5 Suppl 3):S11-145.

24. Bushby K, Finkel R, Birnkrant D, et al. for the DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010 Jan;9(1):77-93.
25. American Congress of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin No. 93: diagnosis and management of vulvar skin disorders. *Obstet Gynecol.* 2008 May;111(5):1243-53. Accessed October 2011.
26. Endocrine Society. Androgen Therapy in Women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2006 Oct;91(10):3697-710. Available at: http://www.endo-society.org/guidelines/final/upload/Androgens_in_Women_CG.pdf. Accessed October 2011.
27. Depo-Testosterone prescribing information. Pfizer. May 2015.
28. Testosterone Gel [Bio-T-Gel] prescribing information. Teva Pharmaceuticals USA. October 2016.
29. Neill SM, Lewis FM, Tatnall FM, Cox NH. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol.* 2010;163:672-82.
30. Miller K, Corcoran C, Armstrong C, et al. Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab.* 1998;83:2712-2725
31. Dolan S, Wilkie S, Aliabadi N, et al. Effects of testosterone administration in human immunodeficiency virus-infected women with low weight. *Arch Intern Med.* 2004;164:897-904.
32. Aveed Prescribing Information. Endo Pharmaceutical Solutions Inc. October 2016.
33. Vogelxo prescribing information. Upsher-Smith Laboratories, Inc. October 2016.
34. Hereditary Angioedema guidelines 2012. *Allergy* 2012;67:147-157
35. WAO HAE guideline 2012. Accessed 6/9/2014@ <http://www.worldallergy.org/UserFiles/file/WAO-HAE-guideline-final-version.pdf>.
36. Summary Minutes of Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. FDA Center for Drug Evaluation and Research. September 17, 2014.
37. Android Prescribing Information. Valeant Pharmaceuticals North America LLC. October 2016.
38. Methitest Prescribing Information. Global Pharmaceuticals, Division of Impax Laboratories Inc. October 2016.
39. Testred Prescribing Information. Valeant Pharmaceuticals North America LLC. May 2015.
40. Management of Erectile Dysfunction (2005). American Urology Association. <http://www.auanet.org/education/guidelines/erectile-dysfunction.cfm>. Accessed October 2014.
41. Natesto Gel prescribing information. Endo Pharmaceuticals Inc. October 2016.
42. deleted
43. Zuraw B, Banerji A, Bernstein J, et al. US Hereditary Angioedema Association Medical Advisory Board 2013. Recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice.* 2013;1:458-467.
44. Bhardwaj N, Craig T. Treatment of hereditary angioedema: a review. *Transfusion* 2014;54:2989-2996.
45. 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 March 2015. Accessed 6.10.2015 at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf>.
46. Danocrine prescribing information. Sanofi-Aventis U.S. LLC December 2011.
47. *JAMA Intern Med.* 2015;175(7): 1187-1196

48. Androgen Deficiency – AIDS/HIV. US Department of Veteran Affairs. Accessed 9/7/2016. <http://www.hiv.va.gov/provider/manual-primary-care/androgen-deficiency.asp>.
49. Critical appraisal of androgen use in hereditary angioedema; a systemic review. *Annals of Allergy, Asthma, & Immunology*. 2015;114: 281-288
50. Testopel prescribing information. Auxilium Pharmaceuticals, Inc. October 2016.
51. FDA approves new changes to testosterone labeling regarding the risks associated with abuse and dependence of testosterone and other anabolic androgenic steroids (AAS). US. Food and Drug Administration. Accessed 10/25/2016. http://www.fda.gov/Drugs/DrugSafety/ucm526206.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
52. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*. September 2009, 94(9):3132-3154
53. Standards of care for the health of transsexual, transgender, and gender nonconforming people V7. The World Professional Association for Transgender Health. 2011.

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

Normal Calcium Values

Normal calcium blood values range: 8.5 to 10.2 mg/dL; may vary slightly among laboratories.³

Gender Dysphoria

Gender Dysphoria (previously named Gender Identity Disorder, sometimes used synonymously with Transsexualism) refers to “discomfort or distress that is caused by a discrepancy between a person’s gender identity and that person’s sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics).”¹ Distress can be severe, resulting in higher prevalence of depression and anxiety.⁴⁻⁸ Global prevalence is difficult to ascertain, but recent estimates approximate that transgender people make up 0.3%-0.5% of the total U.S. population.⁹ Treatment for gender dysphoria varies based on individualized assessment for each patient, but generally includes some combination of psychotherapy, cross-sex hormonal therapy, and sometimes surgical intervention.^{4,5,10-13} The goals of treatment for Gender Dysphoria are to minimize dysphoria and help patients function in society in their desired gender role.¹⁴

The World Professional Association for Transgender Health (WPATH) established criteria for hormone therapy for patients with gender dysphoria. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so.

WPATH guidelines advise that initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional.

The WPATH criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country
4. If significant medical or mental health concerns are present, they must be reasonably well controlled. The presence of co-existing mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to or concurrent with treatment of gender dysphoria.¹⁵

ADDITIONAL INFORMATION REFERENCES

1. World Health Organization. WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children. 2007. Available at: <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>. Accessed October 2011.
2. Shalender B, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2011;95:2536-2559.
3. MedlinePlus. Calcium – blood test: MedlinePlus Medical Encyclopedia. November 2009. Available at: <http://www.nlm.nih.gov/medlineplus/ency/article/003477.htm> Accessed October 2011.
4. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;13(4):165–232.
5. Byne W, Bradley SJ, Coleman E, et al. Report of the American Psychiatric Association task force on treatment of gender identity disorder. *Arch Sex Behav*. 2012;41(4):759–796.
6. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: Results from a longitudinal study. *Psychoneuroendocrinology*. 2014;39:65–73.
7. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013;201(11):996– 1000.
8. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010;72(2):214–231.
9. Gates GJ. How many people are lesbian, gay, bisexual and transgender? 2011.
10. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94(9):3132–3154.
11. Spack NP. Management of transgenderism. *JAMA*. 2013;309(5):478–484.
12. Gooren LJ. Care of transsexual persons. *N Engl J Med*. 2011;364(13):1251–1257.

13. Knezevich EL, Viereck LK, Drincic AT. Medical management of adult transsexual persons. *Pharmacother J Hum Pharmacol Drug Ther.* 2012;32(1):54–66.
14. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/Kalra_comment_01022016_b.pdf
15. Standards of care for the health of transsexual, transgender, and gender nonconforming people V7. The World Professional Association for Transgender Health. 2011.

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.