

Androgenic Agents Review

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Androgenic Agents Review

FDA-Approved Indications

Drug	Manufacturer	Indications
testosterone gel (Androgel [®]) ¹	Abbott Laboratories	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, such as primary or secondary hypogonadism (congenital or acquired)
testosterone gel (Fortesta) ²	Endo Pharmaceuticals	
testosterone gel (Testim [®]) ³	Auxilium	
testosterone transdermal system (Androderm [®]) ⁴	Watson	

Overview

Male hypogonadism is caused by insufficient production of testosterone and is characterized by low serum concentrations. Hypogonadism may present as testosterone deficiency, infertility, or both. Symptoms at presentation will primarily depend on the patient's age at the time of disease onset and can include impotence, decreased libido, fatigue, loss of energy, mood depression, and regression of secondary sex characteristics. Potential risks due to male hypogonadism include osteoporosis, sexual dysfunction, depression, and cardiovascular disease. Approximately 20 percent of men ages 60 to 69 years old and 30 percent of men ages 70 to 79 years old have serum testosterone levels below the normal range.⁵

Causes of hypogonadism are classified as primary or secondary. Conditions resulting in primary male hypogonadism include cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, chemotherapy, or toxic damage from alcohol or heavy metals. Patients usually present with low testosterone levels and elevated follicle stimulating hormone (FSH) and leutinizing hormone (LH) levels. Secondary (hypogonadotropic) hypogonadism includes idiopathic gonadotropin or leutinizing hormone releasing hormone (LHRH) deficiency and pituitary hypothalamic injury from tumors, trauma, or radiation. Testosterone levels are low in patients with secondary hypogonadism, but FSH and LH levels are low or in the normal range.

Testosterone levels are associated with a diurnal rhythm; the highest levels occur during the early morning hours. The testes produce 6-7 mg of testosterone daily, resulting in normal circulating testosterone levels ranging from 300 to 1,000 ng/dL. Testosterone supplementation can maintain secondary sex characteristics, optimize bone density, and restore fertility. Oral administration of testosterone is ineffective due to first-pass metabolism in the liver, so injectable and transdermal methods of delivery are ideal. Transdermal delivery of testosterone is appealing to some patients as it is convenient to use and eliminates frequent office visits often required by injectable testosterone.

The 2002 Treatment guidelines for hypogonadism published by the American Association of Clinical Endocrinologists do not list a preferred method of delivery for testosterone replacement.⁶ Treatment goals are continuation of normal activities of daily living and decreased risk of secondary complications such as infertility, osteoporosis, fatigue, and mood disturbances.

Pharmacology

Topical androgens deliver physiologic amounts of testosterone to the patient, producing testosterone levels correlating with concentrations seen in healthy men. Testosterone is bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40 percent of testosterone in plasma is bound to SHBG and is not biologically active. In addition, SHBG production increases with age, so increasing amounts of testosterone will be bound as men age. Two percent of testosterone is unbound, and the remainder is bound to albumin. The portion bound to albumin is considered to be biologically active since it freely dissociates from albumin.

In many tissues, the activity of testosterone depends on the conversion to dihydrotestosterone (DHT). DHT binds to cytosol receptor proteins; this complex initiates androgenic actions in cell nuclei. DHT is further metabolized to 3 α - and 3 β -androstenediol.

Pharmacokinetics

Drug	T_{max} (hours)	C_{avg} (ng/dL)	t_{1/2} (minutes)
testosterone gel (AndroGel) ⁷	2-4	556-792	10-100
testosterone gel (Fortesta) ⁸	nr	nr	10-100
testosterone gel (Testim) ⁹	4-8	365-612	10-100
testosterone transdermal (Androderm) ¹⁰	7.9	498-621	71

Bioavailability of each product is variable, but most report absorption rates of approximately 10 percent. One small study found testosterone gel preparations (AndroGel, Testim) not bioequivalent; Testim provided higher serum levels than AndroGel when equivalent dosing was used.¹¹

Information regarding the excretion of testosterone is only available for intramuscular administration. By this route, 90 percent of a dose is excreted in the urine as metabolites, and six percent appears unchanged in the feces.

Contraindications/Warnings^{12,13,14,15}

Use of testosterone products is contraindicated in men with carcinoma of the breast or known prostate carcinoma. Testosterone products are Pregnancy Category X and should not be used or handled by women who are pregnant, may become pregnant, or are breastfeeding.

In May 2009, FDA issued a safety alert for testosterone gel products, Androgel and Testim, due to eight reports of children experiencing adverse effects after unintended exposure to testosterone through contact with an individual being treated with these agents.¹⁶ Virilization has been reported in children who were secondarily exposed to testosterone gel. The manufacturers of the testosterone gel products are required to include a boxed warning in the medications' labels related to this safety issue.

Prolonged use of high doses of orally active 17-alkyl androgens such as methyltestosterone has been associated with severe hepatic adverse effects. Testosterone is not known to cause these effects.

Patients diagnosed with benign prostatic hyperplasia (BPH) and treated with androgens are at an increased risk for worsening of signs and symptoms of the disease. Additionally, patients treated with androgenic agents are at increased risk for developing prostatic carcinoma. Surveillance for prostate cancer is also recommended in this population as well as other patients with risk factors.

Sleep apnea, gynecomastia, and edema with or without congestive heart failure are also possible.

Laboratory values requiring periodic monitoring during testosterone therapy include hemoglobin/hematocrit, liver function, prostate specific antigen, cholesterol, and high-density lipoprotein cholesterol (HDL-C).

All testosterone products are Schedule III controlled substances.

Drug Interactions^{17,18,19,20}

Testosterone can cause reductions in blood glucose levels. Patients being treated with testosterone and insulin simultaneously may have lower insulin requirements.

Changes in anticoagulant activity have also been observed in patients receiving both anticoagulant medications and testosterone therapy. It is recommended that patients with concurrent therapy have more frequent monitoring of their prothrombin time (PT) and International Normalized Ratio (INR).

When administered with corticosteroids, testosterone may increase the incidence and extent of edema. Cautious use is advised in patients with hepatic or cardiac disease.

Adverse Effects

Drug	Application Site Reaction	Headache	Acne	Hypertension	Gynecomastia	Increased Hemoglobin/Hematocrit
testosterone gel (Androgel) ²¹	3-5.6	0-4	1-8	0-3	0-3	3-6
testosterone gel (Fortesta) ²²	16.1	nr	nr	nr	nr	nr
testosterone gel (Testim) ²³	2-4	1	<1	1	0-1	1-2
testosterone transdermal (Androderm) ²⁴	>37 (pruritus, blister, erythema, burning)	4	<1	<1	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Special Populations^{25,26,27,28}

Pediatrics

Testosterone products have not been evaluated in pediatric patients. Androderm is approved for use in patients 15 years and older. Androgel, Fortesta, and Testim are not approved for use in patients less than 18 years of age. Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel products.

Pregnancy

The products in this review are Pregnancy Category X.

Dosages

Drug	Dosing	Administration	Availability
testosterone 1% gel (Androgel) ²⁹	5 g daily, preferably in the morning (delivers 5 mg systemically)	Apply to clean, dry, intact skin of the shoulders and upper arms and/or abdomen; do not apply to the genitals	2.5, 5 g packets (30 per package); 75 g pump (2 per package)
testosterone gel (Fortesta) ³⁰	Initiate at 40 mg once every morning. Dosing may be adjusted from 10 mg to 70 mg based on levels two hours after application at days 14 and 35 after start of last adjustment	Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body	In a 60 g canister with metered dose pump delivering 10 mg testosterone in 0.5 g gel per actuation (available in packages of 1, 2 or 3 canisters)
testosterone 1% gel (Testim) ³¹	5 g daily, preferably in the morning (delivers 5 mg systemically)	Apply to clean, dry, intact skin of the shoulders and/or upper arms; do not apply to genitals or abdomen	5 g tubes (30 per package)
testosterone transdermal (Androderm) ³²	5 mg daily (nightly)	Apply to clean, dry skin of the back, abdomen, upper arms, or thighs; do not apply to genitals, bony prominences, or parts of the body that may be subject to prolonged pressure due to sitting or sleeping; rotate sites every seven days	2.5 mg patches (60 per package); 5 mg patches (30 per package)

- Showering or swimming 1-2 hours following Androgel administration should have a minimal effect on absorption.
- Wash hands after applying gels; allow administration area of the gel to dry for several minutes before dressing. Cover the application site once it is dry. Drug can be transferred to others through vigorous skin-to-skin contact.
 - The occlusive backing of Androderm prevents sexual partners from coming into contact with active drug.
- Mild skin irritation with Androderm can be lessened by applying over-the-counter hydrocortisone cream following removal of the patch. Alternately, triamcinolone 0.1% cream may be applied to the skin beneath the drug reservoir of the patch. Use of ointments for this purpose may decrease testosterone absorption.
- Testosterone patches contain 12.3 mg testosterone (2.5 mg patch) and 24.3 mg (5 mg patch).
- Testosterone levels should be measured following initiation of therapy to determine dosage adjustments.

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class.

Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

The method of administration and associated monitoring makes it difficult to perform properly blinded studies with these drugs. Due to the lack of double-blind studies, open-label studies have been included; while these studies may produce accurate results, the study design should be taken into consideration. Fortesta has not been compared to active treatment.

testosterone gel (AndroGel) and testosterone transdermal (Androderm)

Effects of 180 days of treatment with testosterone 1% gel (50 or 100 mg/day) compared to testosterone patch (5 mg/day) on defined efficacy parameters were studied in 227 hypogonadal men.³³ The randomized, parallel group study was double-blinded with respect to gel dose and open-label for the patch group. In the gel groups, the dose was adjusted up or down to 75 mg/day on day 90 if serum testosterone concentrations were below or above the normal male range. No dose adjustment was made in the patch group. Sexual function and mood improved maximally on day 30 of treatment without differences across groups and were maintained for the duration of therapy. Mean muscle strength in the leg press exercise increased by 11-13 kg in all treatment groups by 90 days and did not improve further at the end of treatment. Moderate increases were also observed in arm/chest muscle strength. At 90 days of treatment, lean body mass increased more in the 100 mg/day gel group than in the 50 mg/day gel and patch groups (2.74 versus 1.28 versus 1.20 kg, $p=0.0002$). Beneficial effects were accompanied by anticipated increases in hematocrit and hemoglobin but without significant changes in lipid profile. Skin irritation was reported in 5.5 percent of subjects treated with gel and in 66 percent of subjects in the patch group.

testosterone gel (Testim) and testosterone transdermal (Androderm)

To compare the safety and efficacy of two doses of testosterone 1% gel (50 or 100 mg/day) and a testosterone patch (2 x 2.5 mg), 208 men with confirmed low serum testosterone levels and associated signs and symptoms of hypogonadism were randomized and treated for 90 days.³⁴ The study was double-blinded with respect to the gel dose and open-label for the patch group. Pharmacokinetic profiles were obtained, body composition measured, and mood and sexual function data recorded. Mean increases from baseline to 90 days in testosterone were 12.41, 6.54 and 3.82 nmol/L for the 100 and 50 mg gel groups and the patch ($p<0.05$), respectively. Both doses of gel significantly improved positive and negative mood over baseline; the patch did not ($p<0.05$). All three treatments increased lean body mass. At all sample times, both doses of gel significantly improved sexual performance, motivation, and desire, as well as spontaneous erections. The patch provided improvements from baseline at all sample times for sexual

performance, motivation, and desire, but no statistically significant effect on spontaneous erections. Gel treatment was well tolerated, while patch treatment produced higher rates of application site reactions, resulting in greater study discontinuation.

Hypogonadal male subjects (n=406) reporting one or more symptoms of low testosterone were randomized in an open-label manner to testosterone 1% gel (50 and 100 mg/day), testosterone patch (two 2.5 mg patches), or placebo.³⁵ Primary end points evaluated at 30 and 90 days included significant changes in the frequency of intercourse, nighttime erections, and change in sexual desire measured on a Likert-type scale and calculated as a mean daily score. At day 30, a significant increase from baseline in sexual desire score was noted for those on 100 mg/day gel compared with those on 50 mg/day gel, patch, or placebo (1.2 versus 0.4, 0.7, and 0.4, respectively; $p < 0.0013$). A significant increase from baseline in the frequency of nighttime erections was also noted for those on 100 mg/day gel compared with those on 50 mg/day gel or placebo (51 versus 30, 26 percent, respectively; $p < 0.003$), as well as for the patch versus placebo ($p = 0.0278$). Finally, a significant increase from baseline in the frequency of intercourse was evidenced for those on 100 mg/day gel compared with those on patch or placebo. Similar results were seen for 100 mg/d testosterone gel at day 90 for sexual desire and nighttime erections versus placebo.

In a 90-day open-label study, pharmacokinetics and treatment effectiveness of testosterone 1% gel were compared at 50 and 100 mg/day to a testosterone patch (two 2.5 mg patches) and placebo gel in 406 hypogonadal men.³⁶ Pharmacokinetic profiles were obtained, body composition was measured, and mood and sexual function were monitored. Gel treatments resulted in dose-dependent improvements in all pharmacokinetic parameters. Mean average concentrations at day 90 were 13.8, 17.1, 11.9, and 7.3 nmol/L for 50 mg/day gel, 100 mg/day gel, patch, and placebo, respectively. At day 90, the 100 mg/day treatment improved lean body mass by 1.7 kg and percentage of body fat by 1.2 percent; this was significantly greater than either patch or placebo ($p < 0.05$). Significant improvements in spontaneous erections, sexual desire, and sexual motivation were also evidenced with the 100 mg/day dose in comparison with placebo; the patch also had significant increases with the exception of spontaneous erections. No differences in positive or negative mood were seen between groups. The testosterone patch resulted in a high rate of application site reactions.

Summary

Fortesta is the most recent entry into the topical Androgenic Agents class. Based on available data, there are no apparent differences in efficacy among the various products as all four medications cited produce increased levels of circulating testosterone. The gel formulations of testosterone, however, do demonstrate a lower incidence of adverse reactions related to administration compared to patches. At the present time, long-term studies that evaluate topical treatment options for hypogonadism are lacking.

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