Androgenic Agents, Topical
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
testosterone gel (Androgel®)[1,2]	generic, Abbvie	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®)[3]	generic, Endo	
testosterone gel (Testim®)[4]	generic, Auxilium/Endo	
testosterone gel (Vogelxo®)[5]	generic, Upsher-Smith	
testosterone nasal gel (Natesto™)[6]	Aytu Bioscience	
testosterone solution†[7]	generic	
testosterone transdermal system (Androderm®)[8]	Allergan	

* Safety and efficacy in men with age-related hypogonadism or in males < 18 years old have not been established. Topical testosterone products have different doses, strengths, or application instructions that may result in different systemic exposure. According to the United States (US) Food and Drug Administration (FDA), no testosterone product is indicated for use in men with low testosterone levels who lack an associated medical condition.[9]

† Eli Lilly announced discontinuation of the manufacturer of Axiron; the discontinuation of this brand-name product is not related to safety or efficacy of the drug. Generic versions of the product remain commercially available.

OVERVIEW

Male hypogonadism is caused by insufficient production of testosterone and characterized by low serum concentrations. Hypogonadism may present as testosterone deficiency, infertility, or both.[10] 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. After 30 years of age, testosterone levels in men decrease at rates up to 2% annually.[11]

Causes of hypogonadism are classified as primary, due to failure of the testes, or secondary, due to failure of the hypothalamus or pituitary gland. Either type of hypogonadism, may be caused by an inherited (congenital) or acquired factor. Conditions resulting in primary hypogonadism include cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, chemotherapy, radiation therapy, toxic damage from alcohol or heavy metals, testicular infections (such as mumps) and chromosomal abnormalities such as Klinefelter's Syndrome. Patients usually present with low testosterone levels and elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Secondary (hypogonadotropic) hypogonadism includes idiopathic gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency and pituitary hypothalamic injury from tumors, trauma, or radiation. Testosterone levels are low in patients with secondary hypogonadism, and 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 to 7 mg of testosterone daily, resulting in normal circulating

testosterone levels ranging from 300 to 1,000 ng/dL. Oral administration of testosterone is ineffective due to first-pass metabolism in the liver, therefore 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 (AACE) advise that testosterone replacement therapy can enable the patient to function in a more normal manner and decrease the risk of future problems with fertility, mood disturbances, fatigue, impaired virilization, and osteoporosis. It does not list a preferred method of delivery for testosterone replacement.[12]

The 2018 Endocrine Society (ES) treatment guidelines for hypogonadism recommend a diagnosis of hypogonadism be made only if the patient has symptoms of testosterone deficiency and clearly and consistently low serum testosterone (T) levels, typically based on repeated fasting morning total T levels.[13] Additional diagnostic evaluation should be performed to determine the cause of androgen deficiency. Testosterone treatment is aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density. Treatment goals are continuation of normal activities of daily living and decreased risk of secondary complications such as infertility, osteoporosis, fatigue, and mood disturbances. Target testosterone levels while on therapy should be in the mid-normal range. Monitor serum testosterone, hematocrit, and prostate cancer risk during the first year of treatment. Use of testosterone in men ages ≥ 65 years is not recommended due to unclear risk versus benefit profile in this population. ES also recommends against testosterone therapy in men who are planning fertility in the near future or in patients with breast or prostate cancer. The guidelines recommend against testosterone therapy without further urological evaluation in patients with palpable prostate nodule or induration or prostate specific antigen (PSA) 4 ng/mL or PSA 3 ng/mL in men at high risk of prostate cancer, such as African Americans or men with first-degree relatives with prostate cancer. The guidelines also recommend against testosterone treatment in patients with hematocrit > 48%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms associated with benign prostatic hypertrophy, and uncontrolled or poorly controlled congestive heart failure. While ES provides advantages and disadvantages of each formulation, no preference for any testosterone replacement product is provided. Choice of formulation should be based on patient preference and drug pharmacokinetics, adverse effect profile, treatment burden, and cost. Testosterone transfer to another person who is in close contact is a potential adverse event for the transdermal gel formulations.

The 2018 American Urological Association (AUA) provides a treatment algorithm for evaluating and managing testosterone deficiency.[14] The AUA recommends a total T level < 300 ng/dL based on 2 early morning tests taken on 2 different days to support a diagnosis of low testosterone in symptomatic males. Adjunctive testing (serum luteinizing hormone, serum prolactin, serum estradiol, hemoglobin, hematocrit, PSA) may be considered. Measuring total T level is recommended in patients with a history of unexplained anemia, bone density loss, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, chronic corticosteroids use, and exposure to chemotherapy or testicular radiation. In patients who are candidates for testosterone deficiency, they recommend a cardiovascular (CV) disease risk assessment be performed, and patients at high risk for a CV event be referred for further evaluation. Topical and injectable formulations can be considered without preference for 1 product over another.

In January 2020, the American College of Physicians (ACP) published a clinical guideline on testosterone treatment for adult men with age-related low testosterone.[15] This guideline has been endorsed by the American Academy of Family Physicians (AAFP) and suggest a discussion between clinicians and patients regarding if testosterone therapy should be started for men with age-related low T with sexual dysfunction who want to improve sexual function; patient's preferences as well as benefits and risks of therapy should be considered. It is suggested symptoms be reassessed within 12 months and periodically, and testosterone therapy be discontinued in patients with no improvement in sexual function. As clinical efficacy and safety are comparable for transdermal and intramuscular (IM) testosterone treatment, but costs are lower for IM formulations, these formulations are suggested for improving sexual function when starting tesosterone therapy. It is suggested not to start testosterone therapy for improvement of energy, vitality, physical function, or cognition in men with age-related low T.

PHARMACOLOGY[16,17,18,19,20,21,22,23]

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% 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 3α- and 3β-androstanediol.

PHARMACOKINETICS[24,25,26,27,28,29,30,31]

Drug	T_{max} (hours)	C_{avg} (ng/dL)	$T_{1/2}$ (minutes)
testosterone gel (Androgel 1%)	2	566–792	10–100
testosterone gel (Androgel 1.62%)	8	386–643	10–100
testosterone gel (Fortesta)	4	415–964*	10–100
testosterone gel (Testim)	4–8	365–612	10–100
testosterone gel (Vogelxo)	4–8	365–612	10–100
testosterone nasal gel (Natesto)	0.66	305–537	10–100
testosterone solution	2	456–480	10–100
testosterone transdermal (Androderm)	4–12	300–1,030	10–100

C_{avg} = average serum concentration; $T_{1/2}$ = half-life; T_{max} = time to maximum serum concentration

*Reported for 40 to 70 mg doses

Bioavailability of each product is variable, but most report absorption rates of approximately 10%. One small study found testosterone gel preparations (Androgel, Testim) were not bioequivalent; Testim provided higher serum levels than Androgel when equivalent dosing was used.[32] Vogelxo is considered AB-rated (therapeutically equivalent) to Testim gel.[33]

Information regarding the excretion of testosterone is only available for intramuscular administration. By this route, 90% of a dose is excreted in the urine as metabolites, and 6% appears unchanged in the feces.

CONTRAINDICATIONS/WARNINGS[34,35,36,37,38,39,40,41]

All gel and solution products (Androgel, Fortesta, Testim, Vogelxo, and testosterone solution) carry a boxed warning on virilization of children following secondary exposure; the gel formulations also carry additional safety information regarding secondary exposure in women. The boxed warning does not presently include testosterone patches or testosterone nasal gel, although women and children are cautioned to avoid exposure.

Use of testosterone products is contraindicated in men with carcinoma of the breast or known prostate carcinoma. Testosterone products included in this review are Pregnancy Category X, with the exception of Androgel which has had product labeling updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). These products 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 8 reports of children experiencing adverse effects after unintended exposure to testosterone through contact with an individual being treated with these agents.[42] Virilization has been reported in children who were secondarily exposed to testosterone gel. All of the manufacturers of the testosterone gel and solution 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.

All topical testosterone products should be applied according to the specific administration instructions contained in the application instructions. Products should be applied evenly and not to areas not specified for each product, such as genitals, abdomen, behind the knees, or other locations.

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

The FDA has issued a warning that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions.[43] 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. The FDA has also concluded that there is a possible increased cardiovascular risk associated with testosterone use. This is based on 2 recent studies that suggest an increased risk of cardiovascular events among men prescribed testosterone therapy. Manufacturers are required to clarify the approved uses of these medications and add information to the labeling about a possible increased risk of myocardial infarctions and strokes in patients taking testosterone. In response, AACE/American College of Endocrinology (ACE) issued a position statement stating that the benefits of testosterone replacement in patients with low testosterone outweigh the risks.[44] They further noted that the correlation of cardiovascular risk may be due to low testosterone serving as a marker of cardiovascular disease rather than testosterone supplementation as a causative factor and stated that larger, prospective studies are needed to determine the CV benefits and risks associated with testosterone therapy. A recent systematic review and meta-analysis has not found any significant associations between exogenous testosterone treatment and myocardial infarction, stroke, or mortality; however, the low quality of the current evidence does not rule this out as a possibility.[45]

Androderm, Androgel 1%, Androgel 1.62%, Natesto, Fortesta, Testim, Vogelxo, and testosterone solution all carry an updated warning citing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products. Patients who report or exhibit symptoms of pain, edema, warmth, and erythema in the lower extremity should be evaluated for possible DVT, while those presenting with acute shortness of breath should be evaluated for potential PE. If there is evidence or suspicion of a possible venous thromboembolic event, topical testosterone therapy should be discontinued and appropriate venous thromboembolism (VTE) management initiated.

Androderm, Androgel 1%, Androgel 1.62%, Natesto, Fortesta, Testim, Vogelxo, and testosterone solution also now carry an updated warning regarding potential abuse of testosterone containing products and the need to monitor serum testosterone concentrations if suspected. Testosterone use has been well documented to be subject to abuse, especially when administered at higher doses than recommended for testosterone replacement therapy and when given in combination with other anabolic androgenic steroids. Such abuse may lead to serious cardiovascular and psychiatric adverse reactions. If testosterone abuse is suspected when using these medications, serum testosterone concentrations should be checked and monitored to ensure they are within therapeutic range. Should the abuse involve synthetic testosterone derivatives, testosterone levels may still be found in the normal or subnormal ranges. Patients should be warned of the serious adverse reactions that may occur with abuse of testosterone and anabolic androgenic steroids. Conversely, testosterone and anabolic androgenic steroid abuse should be strongly considered in patients who suddenly present with serious cardiovascular or psychiatric adverse events. All testosterone products are Schedule III controlled substances.

Testosterone nasal gel (Natesto) is not recommended in patients with chronic nasal conditions or alterations in nasal anatomy. In addition, patients should report any signs or symptoms of nasal adverse effects.

Risk Evaluation and Mitigation Strategy (REMS)

At this time, all products in this review, except testosterone patches (Androderm) and testosterone nasal gel (Natesto), require medication guides, however a REMS is no longer required for topical testosterone therapy.

DRUG INTERACTIONS[46,47,48,49,50,51,52,53]

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[54,55,56,57,58,59,60,61]

Drug	Application Site Reaction	Headache	Acne	Hypertension	Gynecomastia	Increased Hemoglobin/ Hematocrit
testosterone gel (Androgel 1%)	3–5.6	0–4	1–8	0–3	0–3	reported
testosterone gel (Androgel 1.62%)	2.1	nr	≤ 2	2.1	nr	2.1
testosterone gel (Fortesta)	16.1	nr	nr	nr	nr	nr
testosterone gel (Testim)	2–4	1	< 1	< 1	0–1	1–2
testosterone gel (Vogelxo)	2–4	1	> 1	1	0–1	1
testosterone nasal gel (Natesto)	nr	3	nr	2–3	nr	< 2
testosterone solution	7–8	5–6	reported	reported	nr	4–7
testosterone transdermal (Androderm)	17	< 3	nr	nr	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.

Nasal adverse effects have been reported with testosterone nasal gel (Natesto). These nasal adverse effects include nasopharyngitis (8.2%), rhinorrhea (7.8%), epistaxis (6.5%), discomfort (5.9%), parosmia (5.2%), nasal scab (5.2%), upper respiratory infection (4.2%), dryness (4.2%), and congestion (3.9%).

SPECIAL POPULATIONS[62,63,64,65,66,67,68,69]

Pediatrics

Testosterone products have not been evaluated in pediatric patients. None of the agents within this class (Androderm, Androgel, Fortesta, Testim, Natesto, Vogelxo, and testosterone solution) are approved for use in patients less than 18 years of age. Exposure may result in acceleration of bone age and premature

closure of epiphyses. 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 with the exception of Androgel which has had product labeling updated to comply with the Pregnancy and lactation Labeling Rule (PLLR). Use of Androgel is contraindicated in pregnant women, as animal studies have shown and based on the mechanism of action, it can cause harm to a developing fetus, including virilization of female fetuses; testosterone is considered to be teratogenic.

Geriatrics

Testosterone transdermal products have not included sufficient numbers of patients 65 years and older in controlled clinical studies to determine whether there is a difference in efficacy and safety from results seen in younger patients. There are an insufficient number of long-term safety studies to assess whether there are variances in prostate cancer or cardiovascular risks between geriatric and younger patients.

DOSAGES[70,71,72,73,74,75,76,77]

Drug	Dosing	Administration	Availability
testosterone 1% gel* (Androgel 1%)	5 g daily, preferably in the morning (delivers 5 mg systemically); Dosing may be increased to 10 mg (by 2.5 mg increments)	Apply to clean, dry, intact skin of the shoulders and upper arms; Do not apply to the genitals	2.5 g, 5 g packets (contains 25 mg or 50 mg testosterone, respectively; 30 packets); 75 g pump with 60 pump actuations delivering 12.5 mg of testosterone per actuation (1.25 g of gel)
testosterone 1.62% gel* (Androgel 1.62%)	40.5 mg (1.25 g of gel) once daily; Dosing may be adjusted between 20.25 mg and 81 mg based on levels drawn at 14 and 28 days after start of therapy	Apply to clean, dry, intact skin of the shoulders and upper arms; Do not apply to the genitals	1.25 g, 2.5 g packets (contains 20.25 mg or 40.5 mg testosterone, respectively; 30 packets); 75 g pump with 60 pump actuations delivering 20.25 mg of testosterone per actuation (1.25 g of gel)
testosterone gel (Fortesta)	Initiate at 40 mg once every morning; Dosing may be adjusted from 10 mg to 70 mg based on levels 2 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
testosterone 1% gel (Testim)	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)

* Abbvie plans to discontinue Androgel 1% pump in the future. Androgel 1% packets and all Androgel 1.62% formulations will continue to be produced.

Dosages (continued)

Drug	Dosing	Administration	Availability
testosterone gel (Vogelxo)	50 mg applied topically once daily at approximately the same time each day; Dosing may be adjusted to 100 mg once daily based on levels drawn at 14 days after start of therapy; maximum dose is 100 mg daily	Apply to clean, dry, intact skin of the shoulders and/or upper arms; Do not apply to genitals or abdomen	In unit-dose tubes or packets containing 50 mg testosterone in 5 g of gel; multiple-dose metered pumps delivering 12.5 mg of testosterone in 1.25 g of gel per actuation
testosterone nasal gel (Natesto)	11 mg total, or 1 pump actuation in each nostril, 3 times a day (once in the morning, once in the afternoon, and once in the evening, about 6 to 8 hours apart); Maximum total daily dose is 33 mg intranasally	Patients should blow nose prior to administration; Actuator should be tipped toward lateral wall of nostril to ensure gel is applied appropriately prior to pressing the pump; Refrain from blowing nose or sniffing for 1 hour following administration; Do not apply to genitals or abdomen	Metered dose pump containing 11 g of gel dispensed as 60 metered pump actuations; each actuation delivers 5.5 mg of testosterone
testosterone solution	Initiate at 60 mg once a day; Dosing may be adjusted 30 mg based on levels drawn 2 to 8 hours after application at days 14 after start or last adjustment	Apply to clean, dry, intact skin of the axilla preferably at the same time every morning; Do not apply to the genitals or other parts of the body	110 mL of topical solution in a metered-dose pump; each pump delivers 30 mg of testosterone in 1.5 mL of solution; each bottle has an applicator top
testosterone transdermal (Androderm)	4 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 7 days	2 mg patches (60 per carton); 4 mg patches (30 per carton) Patches contain 9.7 mg testosterone (delivering 2 mg/day) or 19.5 mg (delivering 4 mg/day)

Prior to initiating therapy, the diagnosis of hypogonadism should be confirmed by measuring serum testosterone concentrations in the morning on at least 2 separate days with the resulting concentrations being below the normal range.

Testosterone levels should be measured, typically 14 days following initiation of therapy, to determine dosage adjustments.

The application sites and dosing recommendations among testosterone replacement products are not interchangeable. Label instructions must be strictly followed to ensure safety and efficacy in use of these products.

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. Should skin-to-skin contact with another person be anticipated, the application site should be washed prior to such contact.

Alcohol based products, including Androgel, Fortesta, Testim, Vogelxo, and testosterone solution are flammable. Patients should be advised to avoid smoking, fire or flame until the dose applied has dried.

Do not swim or shower within 2 hours after application of Androgel 1.62%, Testim, Vogelxo, or testosterone solution and 5 hours after application of Androgel 1% to achieve maximum benefit. Do not swim, shower, or wash the site of administration for Androderm transdermal testosterone for 3 hours following application.

The dosing and administration for Androgel 1% and Androgel 1.62% are not equivalent. Refer to the prescribing information and the table above for the correct dosing of each product.

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.

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% 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.

testosterone gel (Fortesta)

Testosterone gel (Fortesta) was evaluated in a multicenter, 90-day open-label, non-comparative trial of 149 hypogonadal male subjects with body mass index (BMI) ≥ 22 kg/m^2 and < 35 kg/m^2 and 18 to 75 years of age (mean 54.5 years).[78] Patients were screened for a single serum total testosterone concentration of < 250 ng/dL or 2 consecutive serum concentrations < 300 ng/dL. A dose of 40 mg was applied daily to the thighs, with adjustments between 10 mg and 70 mg of testosterone based on serum testosterone levels taken 2 hours after application taken on days 14, 35, and 60. The primary endpoint was the percentage of subjects with a normal testosterone concentration, defined as ≥ 300 to ≤ 1140

ng/dL, at day 90. At day 90, 77.5% of patients had achieved a normal testosterone concentration, and no patient had a maximum testosterone concentration ≥ 2,500 ng/dL on day 90.

testosterone solution

Testosterone solution was evaluated in a multicenter, open label, 120-day trial across 26 centers and including 155 hypogonadal male subjects.[79] The median age for all subjects was 53 years with an age range from 19 to 78 years. Patients were instructed to apply testosterone solution according to the prescribed manner and not to alter current grooming habits. Patients received testosterone solution dose of 60 mg daily during the initial treatment stage on days 1 through 15, and 76.1% of patients achieved an average serum total testosterone level in the normal range, defined as 300 to 1,050 ng/dL. On day 45, doses were adjusted based on their average serum testosterone level, as measured on day 15. Dose adjustment occurred again on day 90, based on the testosterone level taken on day 60. On day 60, 84.8% of subjects had a normal average serum testosterone level. The study concluded on day 120, at which point 84.1% of patients experienced a normal average serum testosterone level.

testosterone gel (Vogelxo)

Testosterone gel (Vogelxo) was evaluated in a randomized, multicenter, multi-dose, active and placebo controlled 90-day trial involving 406 adult males with morning testosterone levels of ≤ 300 ng/dL.[80] The study was double-blind for the doses of testosterone gel and placebo, but open-label for the non-scrotal testosterone transdermal system. During the first 60 days, patients were equally randomized to receive either testosterone gel 50 mg, testosterone gel 100 mg, placebo gel, or testosterone transdermal system. At day 60 of the trial, patients receiving testosterone gel were either maintained at the same dose, or were titrated up or down within their treatment group, based on 24-hour averaged serum testosterone concentration levels previously obtained on day 30. Of 192 hypogonadal males in the trial who were appropriately titrated with testosterone gel and who had generated sufficient data for analysis, 74% achieved an average serum testosterone level within the normal range (300 to 1,000 ng/dL) by treatment day 90.

testosterone nasal gel (Natesto)

Testosterone nasal gel was studied in an open-label, multicenter, 90-day phase 3 trial in 306 hypogonadal men.[81] Testosterone was administered intranasally either 2 or 3 times daily. During the treatment period (days 1 to 90), 78 patients were treated with 33 mg of testosterone daily. Of these, a total of 73 men were included in the statistical evaluation of efficacy on day 90 based on the intent-to-treat (ITT; n=73) population with last observation carried forward (LOCF). A total of 90% of these patients had an average serum testosterone concentration (C_{avg} within the normal range [300 to 1,050 ng/dL] on day 90 (primary endpoint). The percentage of patients with C_{avg} below the normal range (< 300 ng/dL) on day 90 was 10% and no subject had a C_{avg} value exceeding 1,050 ng/dL.

testosterone transdermal patch (Androderm)

Testosterone transdermal (Androderm new formulation) was evaluated in a comparative trial to evaluate dosing and titration of the new 2 mg/day and 4 mg/day systems in 40 males with hypogonadism in a clinic setting.[82] Mean age was 55 years (range 34 to 76 years). Patients had previously been stabilized on either Androderm 5 mg; Androgel 2.5 g, 5 g, 7.5 g, 10 g; or Testim 2.5 g or 5 g daily prior to the trial. Testosterone transdermal was applied nightly at 2,000 hours for 14 days. Dosing was titrated based on serum concentrations taken the morning of Day 8. Of patients formerly receiving Androderm 5 mg/day

(n=11) 10 subjects remained at the 4 mg/day dosing and 1 was titrated down to the 2 mg/day dosing. At the 28-day mark, 97% of trial subjects had serum testosterone C_{avg} measurements within the normal range for the dosing period.

testosterone gel (Androgel) and testosterone transdermal patch (Androderm)

Effects of 180 days of treatment with testosterone 1% gel (50 or 100 mg/day) compared to testosterone patch (5 mg/day, old formulation) on defined efficacy parameters were studied in 227 hypogonadal men.[83] 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, as monitored by questionnaire, 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 to 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 1.2 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% of subjects treated with gel and in 66% of subjects in the patch group.

testosterone gel (Testim) and testosterone transdermal patch (Androderm)

To compare the safety and efficacy of 2 doses of testosterone 1% gel (50 or 100 mg/day) and a testosterone patch (2 x 2.5 mg, old formulation), 208 men with confirmed low serum testosterone levels and associated signs and symptoms of hypogonadism were randomized and treated for 90 days.[84] 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 3 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 1 or more symptoms of low testosterone were randomized in a double-blinded manner to testosterone 1% gel (50 and 100 mg/day) or placebo, and an open-label manner to testosterone patch (two 2.5 mg patches, old formulation).[85] Subjects on the testosterone gel could be titrated up or down at day 60 on the basis of their day 30 serum testosterone level. Primary end points evaluated at 30 and 90 days included significant changes in the frequency of intercourse, nighttime erections, and 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%, 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, old formulation) and placebo gel in 406 hypogonadal men.[86] 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 compared with the testosterone patch and placebo. 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%; 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

Testosterone supplementation may be considered in men with symptoms of testosterone deficiency and confirmed low serum testosterone (T) levels based on morning testosterone levels. The 2020 American College of Physicians clinical guideline on testosterone treatment for adult men with age-related low T suggests testosterone therapy can be started for men with age-related low T with sexual dysfunction who want to improve sexual function, however it is suggested not to start testosterone therapy for improvement of energy, vitality, physical function, or cognition. Based on available data, there are no apparent differences in efficacy among the various products within this class, as all medications produce increased levels of circulating testosterone, and all carry the same indication.

The gel and solution formulations of testosterone, however, do demonstrate a lower incidence of adverse reactions related to administration compared to the patches. The nasal gel also has a lower incidence of administration related adverse reactions. However, it does have a greater number of nasal adverse effects and should not be used in patients with chronic nasal conditions. Long-term studies that evaluate topical treatment options for hypogonadism are lacking. The 2018 Endocrine Society testosterone therapy guideline recommends selecting a testosterone regimen on the basis of the patient's preference, pharmacokinetics profile, treatment burden, and cost.

Androgel is available as a 1% and a 1.62% strength. Other gel formulations include Fortesta, Testim, and Vogelxo. Testosterone is also available as a generic topical solution, as brand-name Axiron topical solution was discontinued in 2019. Androderm is available as a transdermal patch. Natesto offers a nasal gel formulation as an alternative to topical gels or solutions and testosterone patches. Several products in this class are available as a generic. All testosterone products are Schedule III controlled substances.

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