Therapeutic Class Overview
Androgens (testosterone)

Therapeutic Class

- **Overview/Summary:** The topical testosterone products listed in Table 1 are approved by the Food and Drug Administration for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with testosterone pellets also having an indication to stimulate puberty in carefully selected males with clearly delayed puberty.[1-10] There are few differences between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product available as a transdermal patch. AndroGel®, Fortesta®, Natesto®, Testim®, and Vogelxo® are available in gel preparations, while Axiron® is formulated as a topical solution. These products are available as metered-dose pumps or single-use packets/tubes. Natesto® is the only nasal gel available in the form of a metered dose pump. Striant® is a mucoadhesive buccal tablet system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is an implantable pellet that consists of crystalline testosterone. It is a cylindrically shaped pellet, 3.2mm (1/8 inch) in diameter and approximately 8-9mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone over three to six months for a long acting androgenic effect. Androderm® is applied at night, while the topical gels and solution are generally applied in the morning.[1-10] A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, may reduce skin irritations that develop.[1] The labeling of testosterone solution and gels, excluding testosterone nasal gel, include a Black Box Warning regarding the risk of virilization of female sexual partners that has been reported with male use of topical testosterone gels and solution.[2-7] The occlusive backing film on Androderm® prevents the partner from coming in contact with the active material in the system, and therefore the warning is not included on this product.[1] Currently, only AndroGel® has an A-rated generic formulation.

  Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.[12-16] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[13] Secondary hypogonadism, known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary. This occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[13] Combined primary and secondary hypogonadism may occur and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[15] Male hypogonadism may manifest as testosterone deficiency with or without infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[12-17]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Testosterone (Androderm®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Androderm®: 2 mg/day patch 4 mg/day patch	-
Testosterone (AndroGel®*)	Hypogonadism in males, primary (congenital or acquired) and	AndroGel® 1%: Metered-dose pump:	a

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	hypogonadotropic hypogonadism in males (congenital or acquired)	12.5 mg testosterone/actuation Unit-dose packet: 50 mg testosterone/packet AndroGel® 1.62%: Metered-dose pump: 20.25 mg/actuation Unit-dose packet: 20.25 mg/packet	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump: 30 mg/actuation	-
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump: 10 mg/actuation	-
Testosterone (Natesto®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Natesto®: Intranasal gel metered-dose pump: 5.5 mg/actuation	-
Testosterone (Striant®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Striant®: Buccal mucoadhesive system: 30 mg	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes: 50 mg/tube)	-
Testosterone (Testopel®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired); stimulate puberty in carefully selected males with clearly delayed puberty	Testopel®: Implantable pellet: 30 mg	-
Testosterone (Vogelxo®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Vogelxo®: Metered-dose pump: 12.5 mg/actuation Unit-dose packet: 50 mg/packet Unit-dose tube: 50 mg/tube	-

*A-rated generic available in at least one dosage form or strength

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Evidence-based Medicine

- Topical and miscellaneous testosterone products have been evaluated in several clinical trials.[19-31]
- The efficacy of testosterone nasal gel was evaluated in an unpublished, 90-day, open-label, multicenter study of 306 hypogonadal men 18 years of age and older. Individuals were instructed to self-administer one spray of testosterone intranasally either two or three times daily. The primary endpoint assessed was the percentage of individuals with an average serum total testosterone concentration within the range of 300 to 1,050 ng/dL on Day 90. Of the 306 men in the study, results were only available for 73 hypogonadal men who had received the nasal gel three times daily. On Day 90, 90% of these individuals had an average concentration within the established normal range, 10% were below normal and no individuals were found to be above the desired range.[8]
- The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[9]
- The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Mean testosterone significantly increased and luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits, and had returned to pre-implantation levels by week 24 ($P<0.001$ for mean testosterone and LH levels at week one, week four and week 12 visits; $P=0.58$ and $P=0.87$ for mean testosterone and LH at week 24 respectively). Prostate-specific antigen levels remained unchanged for the duration of the study.[19]
- Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[20-23]
- In an open-label study, Axiron® topical solution applied to the axilla provided a serum testosterone level in the normal range for 84.1% of patients after 120 days of treatment.[17] Results from a second open-label study reported that 76.2% of men achieved a mean serum testosterone level within the normal physiologic range following 35 days of treatment with Fortesta®.[27]
- In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[30] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone.
- Blick et al evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, but non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS ($P\leq0.05$) and remained stable in men with HIV/AIDS during the twelve months of follow-up.[31]
- A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al. The overall response rate was 57% ± 2.3% (203 of 356 cases). Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant ($P<0.001$).[32]

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Key Points within the Medication Class

- According to Current Clinical Guidelines[13-16]:
  - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.
  - The oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes, and hepatic side effects, but may be considered when other agents are not suitable.
  - The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden and cost.
  - The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Treatment guidelines do not recommend one topical preparation over another.

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Therapeutic Class Review
Androgens (testosterone)

Overview/Summary

Testosterone products are available in a number of dosage forms including oral administration, intramuscular injection, topical gel, transdermal patch, a topical solution, a subcutaneous implantable pellet and a buccal delivery system. This review will focus on the topically administered testosterone products including Androderm®, AndroGel®, Axiron®, Fortesta®, Natesto®, Striant®, Testim® and Vogelxo® and the implant pellet Testopel®. All of these products are approved by the Food and Drug Administration (FDA) for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) with Testopel® also being indicated for stimulation of puberty in males who clearly have delayed puberty. All testosterone products are controlled substances and have all been assigned as Schedule III products.[1-10]

Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad (testes) function.[12-16] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[13] Secondary hypogonadism (hypogonadotropic) results from defects in the hypothalamus or pituitary and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[13] Combined primary and secondary hypogonadism may occur, and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[15] Male hypogonadism may manifest as testosterone deficiency with or without infertility. As a result, appropriate disease classification is necessary since fertility can be restored with appropriate androgen stimulation in individuals with secondary hypogonadism, but not in most individuals diagnosed with primary hypogonadism.[15] Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[12-17]

There are few differentiating factors between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product that is available as a once-daily transdermal patch that is applied at night. Natesto® is the only nasal gel available in the form of a metered dose pump. AndroGel®, Testim®, Fortesta® and Vogelxo® are available in gel preparations and Axiron® is formulated as a topical solution. These products are available as meter-dosed pumps and single-use tubes and are all applied once daily, generally in the morning. Striant® is formulated as a buccal mucoadhesive system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is a pellet that consists of crystalline testosterone. It is cylindrically shaped, 3.2mm (1/8 inch) in diameter and approximately 8 to 9 mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone for a long acting androgenic effect. A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, applied after the transdermal system has been removed, may reduce skin irritations that may develop. [1-10] Currently, only AndroGel® has an A-rated generic formulation.

According to current consensus guidelines, intramuscular (IM) and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.[14-17] The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential

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development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Moreover, the guidelines do not recommend one topical preparation over another.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Testosterone (Androderm®, AndroGel®*, Axiron®, Fortesta®, Natesto®, Striant®, Testim®, Testopel®, Vogelxo®)	Androgens	a

*A-rated generic exists in at least one formulation or strength

Indications

Table 2. Food and Drug Administration Approved Indications[1-10]

Indication	Testosterone
Hypogonadism, primary (congenital or acquired in males)	a (all)
Hypogonadotropic hypogonadism in males (congenital or acquired)	a (all)
Stimulate puberty in carefully selected males with clearly delayed puberty	a (Testopel®)

In addition to the Food and Drug Administration-approved indications, testosterone has been used off-label for male infertility, osteoporosis and weight gain. Testosterone has also been used concomitantly with estrogens for the management of vasomotor symptoms associated with menopause and in postmenopausal women with decreased sexual desire.[11]

Because of their anabolic and androgenic effects on performance and physique, androgens have been misused and abused by athletes, bodybuilders, and others.[18] Due to the potential risk of serious adverse health effects, androgens should not be used to enhance athletic performance. Testosterone replacement therapy is also not indicated for the treatment of erectile dysfunction in men with normal serum testosterone concentrations.

Pharmacokinetics

Table 3. Pharmacokinetics[1-11]

Drug	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Testosterone, transdermal (buccal system, gels, implant, patch, solution)†	10 (gel)	2 to 8 (gel); 8 (patch);	Urine (90)‡	Estradiol, Dihydro-testosterone	0.2 to 1.7*

* Half-life not reported for all products but range of 10 to 100 minutes referenced.
† Any product not listed did not have a value reported.
DHT=dihydrotestosterone.
‡ Based on intramuscular administration.

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Clinical Trials

Topical and miscellaneous testosterone products have been evaluated in several clinical trials and are summarized in Table 4.[19-31]

The efficacy of testosterone nasal gel was evaluated in an unpublished, 90-day, open-label, multicenter study of 306 hypogonadal men 18 years of age and older. Individuals were instructed to self-administer one spray of testosterone intranasally either two or three times daily. The primary endpoint assessed was the percentage of individuals with an average serum total testosterone concentration within the range of 300 to 1,050 ng/dL on Day 90. Of the 306 men in the study, results were only available for 73 hypogonadal men who had received the nasal gel three times daily. On Day 90, 90% of these individuals had an average concentration within the established normal range, 10% were below normal and no individuals were found to be above the desired range.[8]

The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Results from the open-label trial showed that mean testosterone levels significantly increased from pre-implantation values at week one, week four and week 12 visits (P<0.001 at all time points) and had returned to pre-implantation levels by week 24 (P=0.58). In addition, luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits (P<0.001 at all time points) and returned to pre-implantation levels by week 24 (P=0.87). Prostate-specific antigen levels remained unchanged for the duration of the study. Improvements in symptoms were determined with multiple questionnaires including International Index of Erectile Function (IIEF)-erectile function domain and International Prostate Symptom Score (IPSS). Mean IIEF scores were not significantly different at the end of the study when compared with baseline (P=0.56). Although the severity of voiding symptoms, as assessed by IPSS, decreased at all time points compared with pre-implantation scores, there was not a statistically significant difference (P=0.76, P=0.92, P=0.68, respectively). Overall, implanted testosterone pellets were found to be well tolerated.[19]

Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[20-23]

In a randomized, multidose, multicenter, active-controlled study comparing two doses of testosterone gel (Testim® 50 mg and 100 mg) and a transdermal testosterone system, Testim® 100 mg produced significantly higher serum levels of testosterone, free testosterone and dihydrotestosterone (DHT).[20] All three treatments produced significant increases in lean body mass (LBM) while only Testim® 100 mg produced significant decreases in percentage of fat. Significant differences between treatment groups were seen in the alleviation of negative mood and improvements in spontaneous erections favoring Testim® over transdermal testosterone for both measures. All three treatment groups produced significant improvements in sexual motivation, sexual desire and sexual performance. The transdermal testosterone system was associated with a higher incidence of treatment-emergent adverse events. In a second study comparing two doses of Testim®, a transdermal testosterone patch (Androderm®) and placebo, all treatment groups produced similar increases in serum testosterone and DHT levels.[21] All treatment groups produced increases in LBM, however the Testim® 100 mg group increased LBM to a significantly greater degree compared to the Androderm® and placebo groups (*P*<0.05 for each measure). The use of both Testim® and Androderm® resulted in significant decreases in fat mass compared to placebo. Only Testim® 100 mg produced significant improvements in sexual function over placebo. There were no significant differences among treatment groups in improving mood, and Androderm® was associated with more treatment-emergent adverse events.

When two doses of a testosterone gel (AndroGel®) were compared to Androderm®, AndroGel® 100 mg was associated with significantly higher levels of testosterone and free testosterone compared to AndroGel® 50 mg and Androderm®.[22] There were significant increases in serum DHT levels with both doses of AndroGel® compared to Androderm®. The discontinuation rate, mostly due to adverse skin reactions, was significantly

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greater in the Androderm® group. In a study by Wang et al, AndroGel® and Androderm® average serum testosterone levels increased greatest with AndroGel® 100 mg (*P* values not reported).[23] A decrease in percent body fat and total fat mass occurred in all treatment groups, however, this was only significant for AndroGel®. All treatment groups produced significant improvements in sexual function. Treatment with AndroGel® resulted in significant increases in prostate specific antigen levels. Skin irritation at the application site occurred in 65.8, 5.3 and 5.7% of patients in the Androderm®, AndroGel® 100 mg and 50 mg groups. This study also demonstrated that all treatments caused a significant increase in hemoglobin (Hgb) and hematocrit (Hct) but had no overall effects on lipid profiles or blood chemistries.

In an extension study, patients treated with three doses of AndroGel® were observed for a period of 36 months.[24] Long-term treatment with AndroGel® maintained increased levels of serum testosterone and improvements in sexual function, positive mood and body composition. A gradual, but significant improvement in hip and spine bone mineral density was also observed. Increases in Hgb and Hct plateaued at 12 months and clinically insignificant increases in high-density lipoprotein cholesterol, serum creatinine and total bilirubin were seen. Serum levels of prostate specific antigen showed no further significant increases past six months of treatment. Treatment-emergent adverse events included application site reactions (7.4%), acne (7.4%) and gynecomastia developed in eight patients.

Grober et al evaluated the efficacy of changing from one testosterone gel preparation to another after suboptimal response.[25] Of the 370 hypogonadal men on testosterone replacement therapy, 20% of men underwent a brand substitution due to initial suboptimal response. Among men switching from AndroGel® to Testim® a total of 69, 58 and 65% experienced improvements in libido, erectile function and energy levels, respectively. The rates of improvement for these same parameters among men switching from Testim® to AndroGel® were 46, 39 and 46%, respectively. Changing from AndroGel® to Testim® was reported to have resulted in improved clinical and biochemical responsiveness. Changing from Testim® to AndroGel® eliminated or minimized unwanted side effects (primarily scent).

The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[9]

In a multicenter, randomized control trial by Korbonits et al, testosterone buccal 30 mg applied twice daily was compared to the testosterone transdermal patch (Andropatch® [not commercially available in the U.S.] or Androderm®) 5 mg once-daily for seven days.[26] The investigators concluded (results not reported) testosterone buccal was non-inferior to the testosterone patch formulation. At all measured time points, the mean testosterone levels were within the established physiological range among patients receiving the buccal formulation compared to five measured time points falling outside of this range among patients receiving the patch formulation. Also, the proportion of patients with levels outside the physiological range was lower in the buccal group compared to the patch group for both the mean (0 to 24 hour) and minimum testosterone levels (the differences; $P<0.001$ for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch ($P<0.00001$). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group; whereas only the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group. The most common adverse events reported among both groups were application site reactions.

Dobs et al evaluated the efficacy of testosterone topical gel (Fortesta®) 40 mg applied to the thighs once daily in varying doses depending upon serum testosterone response in a multicenter, open-label, non-comparative trial.[28] At study endpoint (day 90), the mean serum total testosterone concentration over 24 hours (C_{avg} 0 to 24hr ± SD) for the 129 individuals with data available for analysis, was 438.56 ± 162.51 ng/dL, a total of 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal

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physiological range of ≥300 and ≤1140 ng/dL (95% CI, 70.3% to 84.7%). By day 35, 76.2% (95% CI, 68.8% to 83.6%) of patients had reached the primary endpoint and on day 90, 22.5% of patients had a total testosterone level <300 ng/dL. The most commonly reported adverse events were skin reactions, upper respiratory infections, and sinusitis. Skin reactions considered possibly/probably related to study medication were reported in 16.1% of patients, of which 79.2% were determined to be mild in severity.

A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al[29]. The overall response rate was 57% ± 2.3% (203 of 356 cases). The etiology of impotence was reported in 11 of the articles; of which nine included stratified response rates based upon primary versus secondary etiology. Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant (*P*<0.001). Further analysis evaluated the delivery method [transdermal patch, intramuscular injection, and oral routes of administration] and found that intramuscular and oral formulation were similar with a response rate of 51.2% ± 2.9% versus 53.2% ± 5.6, respectively (independent sample z test for proportions weighted by study sample size; *P*=0.86). Conversely, the transdermal formulation was significantly different than intramuscular formulation with a response rate of 80.9% ± 5.9% (independent sample z test for proportions weighted by study sample size; *P*<0.001). The response rate for transdermal delivery was also significantly different from oral delivery (independent sample z test for proportions weighted by study sample size; *P*<0.001). Only five of the 16 trials evaluated reported response rates for both placebo and testosterone and had randomized crossover evaluations. There was a mean response of 16.7% versus 65.4% for the placebo and testosterone arms, respectively (two-sample z test for proportions weighted by study sample size z=5.9; *P*<0.0001). The observed difference was 48.7% (range 16.7% to 65.4%, 95% CI, 32.6 to 64.8) in favor of testosterone.

In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[30] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone. This study also showed that >50% men require doses larger than the traditional starting dose, which is in agreement with previous data.

Blick et al recently evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) patients utilizing the Testim Registry in the United States (TRiUS)[31] In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, both non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS (P≤0.05) and remained stable in men with HIV/AIDS during the twelve months of follow-up.

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Hypogonadism				
Kaminetsky et al[19] (UUA215) Testosterone pellets implanted dose based on baseline testosterone level and BMI (UUA216) Testosterone pellets implanted dose based on peak testosterone level during UUA215	(UUA215) OL Men ≥18 years of age with primary or secondary hypogonadism, historical serum testosterone concentration of ≤315 ng/dL and ≥ three months of testosterone replacement therapy (UUA216) ES, OL Patients who enrolled in UUA215 and had a total testosterone level ≤315 ng/dL at the end of the study	(UUA215) N=30 24 weeks (UUA216) N=24 24 weeks	Primary: Mean testosterone, LH, IIEF score, IPSS score and adverse events Secondary: Not reported	Primary: (UUA215) The preimplantation mean testosterone level was 216 ng/dL. Mean testosterone levels were significantly higher at the week one, week four, and week 12 visits (845 ng/dL, 838 ng/dL, 524 ng/dL, respectively) compared with the preimplantation level (P<0.0001 at all time points). Mean testosterone at the conclusion of the study (week 24, or earlier for subjects who opted for a second implant when testosterone levels were <315 ng/dL) had returned to preimplantation levels (232 ng/dL, P=0.58). Mean LH was reduced from a preimplantation level of 5.1 ng/dL to 1.3 ng/dL, 0.2 ng/dL, and 0.6 ng/dL at week one, week four, and week 12, respectively (P<0.0001 at all time points). By the end of the study, mean LH had returned to pre-implantation level (5.2 ng/dL, P=0.87). Mean IIEF scores were not significantly higher compared with baseline (15.9) at the end of the study (18.5, P=0.56). However, there was a significant difference in IIEF scores compared with baseline at week four (20.1, P=0.003) and week 12 (20.9, P=0.001). The severity of voiding symptoms, as assessed by IPSS, decreased at all time points compared with pre-implantation scores, but did not reach statistical significance (P =0.76, P =0.92, P =0.68 at weeks 4, 16 and 24, respectively). (UUA216) Mean testosterone levels increased from 201 ng/dL at the time of implant to 743 ng/dL at week four (P <0.0001), and all subjects had increased testosterone levels at this time point compared with baseline. Although mean testosterone levels had fallen below 315 ng/dL in the 22 subjects for whom week 16 data are available, they were still significantly higher at this time point compared with the time of implant (200 ng/dL vs 275 ng/dL, P=0.003). Mean testosterone levels at the end of the study were similar to those at the time of implant (200 ng/dL vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				214 ng/dL, P=0.53). All subjects had testosterone levels >315 ng/dL at week four, and nearly a third (31.8%) were still above 315 ng/dL at week 16. (UUA215 and UUA216) Testosterone pellets were generally well tolerated. Most investigator-reported adverse events were mild and transient, and included pain, tenderness, erythema/redness, swelling, and ecchymosis. In both the UUA215 and UUA216 protocols, these symptoms were most commonly observed on the day of implantation and at week one visit. Secondary: Not reported
McNicholas et al[20] Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Andropatch®*) 2.5 mg two patches daily in the morning	AC, DB, MC, OL, RCT Hypogonadal men, 31 to 80 years old, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone	N=208 90 days	Primary: 24-hour PK profiles at 30, 60 and 90 days; treatment effectiveness as measured by body composition, mood, and sexual function data at 30, 60 and 90 days; safety Secondary: Not reported	Primary: At 90 days, mean increases in serum testosterone levels were significant for testosterone gel 100 mg (12.41 nmol/L) over testosterone gel 50 mg (6.54 nmol/L; *P*<0.05) and testosterone patch (3.82 nmol/L; *P*<0.001). Results at 30 and 60 days were consistent with those at 90 days. The same results were also seen with the mean increase from baseline in free testosterone levels. At 90 days, the mean change in DHT levels with testosterone gel 100 mg were significant over testosterone gel 50 mg (*P*<0.05) and testosterone patch (*P*<0.001). In addition, the mean change in DHT levels with testosterone gel 50 mg was also significant over testosterone patch at 90 days (*P*<0.001). Results at 30 and 60 days were consistent with those at 90 days. Significant within-treatment group changes in LBM were seen for all three treatment groups; 0.9 kg (*P*<0.05), 1.5 kg (*P*<0.001) and 1.0 kg (*P*<0.05) for testosterone gel 50 mg, testosterone gel 100 mg, and testosterone patch, respectively. Significant within-treatment group mean changes in percentage fat were only seen with testosterone gel 100 mg (–0.7; *P*<0.05). There were no statistically significant changes in BMD within any of the three treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant differences in improvement in positive mood were seen among the three treatment groups. There were significant differences between treatment groups at 90 days in the alleviation of negative mood favoring testosterone gel over the testosterone patch (*P*<0.05). At 90 days there were significant within-treatment group improvements from baseline in all three groups in sexual motivation, sexual desire, and sexual performance (*P*<0.05). Both testosterone gel groups had a statistically significant within-treatment improvement in spontaneous erections at all times from baseline (*P*<0.05). Testosterone patch produced no significant improvement in spontaneous erections at any time. The incidence of treatment-emergent adverse events was 35% for testosterone gel 50 mg, 29% for testosterone gel 100 mg, and 63% for testosterone patch groups. The most commonly reported adverse events were erythema, irritation, and reactions at the application site. Secondary: Not reported
Steidle et al[21] Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Androderm®) 2.5 mg 2 patches daily in the	AC, DB, MC, OL, PC, RCT Hypogonadal men, 20 to 80 years old, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone	N=406 90 days	Primary: Periodic 24-hour PK profiles; effect of normalizing serum testosterone on body composition, sexual function, mood and BMD; safety Secondary: Not reported	Primary: At 30 days, all treatment groups had increased mean serum testosterone and DHT concentrations. Testosterone gel 100 mg had a significant increase in mean changes in testosterone concentrations over the testosterone patch (*P*<0.001). Testosterone gel 50 mg and 100 mg resulted in significant increases in mean changes in DHT concentrations compared to the testosterone patch (*P*<0.001 for each comparison). By 90 days, similar results were seen across treatment groups. At 90 days, mean change in LBM was 1.5±4.5, 1.7±2.6, 0.9±1.8 and 0.6±1.8 kg for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch, and placebo, respectively. Increases in LBM were significantly higher for testosterone gel 100 mg than the testosterone patch and placebo (*P*<0.05 for each comparison). With the exception of placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morning vs placebo				treatment, all treatments resulted in a significant decrease in FM compared to placebo (*P*<0.01). At 90 days, when compared to placebo, testosterone gel 100 mg had significant improvements in spontaneous erections (*P*<0.001), sexual motivation (*P*<0.05), sexual desire (*P*<0.01), and sexual performance (*P*<0.05). No other treatment groups had significant improvements compared to placebo. All treatments resulted in mean improvements from baseline in both positive and negative mood scores with no significant differences among the treatment groups. The incidence of treatment-related adverse events was 29.1, 36.9, 62.7, and 40.4% for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch, and placebo, respectively. At 90 days, clinically notable decreases in total-C, LDL-C, and HDL-C were seen with testosterone gel 100 mg (*P* value not reported). Increases in Hgb and Hct were the highest with testosterone gel compared to The testosterone patch and placebo. Increases in PSA values were highest in the testosterone patch group (6.6%). Secondary: Not reported
Swerdloff et al[22] Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Serum testosterone and free testosterone levels at 0, 1, 30, 90, and 180 days; safety; serum DHT, E_2, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days Secondary:	Primary: At 30 and 90 days, testosterone gel 100 mg produced significantly higher C_{avg} testosterone levels over testosterone 50 mg and testosterone patch (27.46±1.12 nmol/L vs 19.17±1.06 and 14.46±0.68 nmol/L, respectively; *P*=0.0001). At 180 days, serum testosterone levels and PK parameters were similar to those on days 30 and 90 in those patients who continued their initial randomized treatment. Patients switched to testosterone gel 75 mg had a C_{avg} testosterone level of 20.84±1.76 nmol/L at 180 days. This value was between the 180 day C_{avg} testosterone levels achieved with testosterone gel 50 mg (19.24±1.18) and testosterone gel 100 mg (24.72±1.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
testosterone patch (Androderm®) 2.5 mg 2 patches daily At 60 days, men with serum testosterone levels <10.4 nmol/L who were applying AndroGel® 50 mg and men with serum testosterone levels >34.7 nmol/L who were applying AndroGel® 100 mg were instructed to apply AndroGel® 75 mg once daily for days 91 through 180.			Not reported	PK parameters of serum free testosterone levels on days one, 30, 90 and 180 mirrored those of serum testosterone levels. The free testosterone levels in the testosterone gel 100 mg group was 1.4- and 1.7-fold higher than the testosterone gel 50 mg and testosterone patch groups (*P*=0.001). The discontinuation rate at 90 days for the testosterone patch (27.6%) was significantly higher than testosterone gel 50 and 100 mg (8.2% and 6.4%, respectively; *P*=0.0002). Most patients discontinued treatment due to adverse skin reactions. Throughout the 180 days, increases in serum DHT levels were significant with testosterone gel 50 and 100 mg over the testosterone patch (*P*=0.0001). Mean serum increases to stable levels of E_2 occurred in 9.2, 30.9, and 45.5% of patients in the testosterone patch, testosterone gel 50, and testosterone gel 100 mg groups, respectively (*P*=0.001). All three treatment groups showed a small decrease in serum SHBG levels (*P*=0.0046). The mean percent suppression of serum LH levels was the smallest with testosterone patch (30 to 40%), intermediate with testosterone gel 50 mg (55 to 60%), and greatest with testosterone gel 100 mg (80 to 85%; *P*<0.01). The suppression of serum FSH paralleled that of serum LH levels. Secondary: Not reported
Wang et al[23] Testosterone gel (AndroGel®) 50 mg daily vs	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old,	N=227 180 days	Primary: Mean change from baseline in serum testosterone concentrations, body composition, and	Primary: On day 90 the average serum testosterone concentration with testosterone gel 100 mg (27.46±1.12 nmol/L) was 1.4-fold higher than testosterone gel 50 mg (19.17±1.06 nmol/L) and 1.9-fold higher than the testosterone patch (14.46±0.68 nmol/L; *P* value not reported). On day 180 average serum testosterone concentrations for the treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg two patches daily At 90 days, dose adjustments were made in the AndroGel® groups based on the pre-application serum testosterone levels on day 60. Twenty subjects in the AndroGel® 50 mg group had their dose increased to 75 mg and 20 subjects in the AndroGel® 100 mg group had their dose reduced to 75 mg.	morning serum testosterone level ≤10.4 nmol/L at screening		muscle strength at 90 and 180 days; mean change from baseline in sexual function and mood at 30, 60, 90, 120, 150 and 180 days; degree of skin irritation; mean change from baseline in serum PSA levels at 30 and 90 days; mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries Secondary: Not reported	were 24.72±1.05 nmol/L, 19.24±1.18 nmol/L and 14.14±0.88 nmol/L, respectively. The percent body fat and FM decreased in all treatment groups but was only significant with testosterone gel. At 90 days the total FM was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (*P*=0.0065 and *P*=0.0001, respectively). At 180 days the total FM decreased further with testosterone gel 100 mg (*P*=0.008). At 90 days, the percent body fat was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (*P*=0.0018 and *P*=0.001) and remained significant at 180 days. Significant increases in arm and leg muscle strength were seen in all three treatment groups without intergroup differences on days 90 and 180 (*P* values compared to baseline ranged between 0.0001 to 0.08). All subjects, regardless of treatment group, showed significant improvement in sexual motivation (*P*=0.0001), sexual desire (*P*=0.0001), sexual performance (*P*=0.0001), self-assessment of satisfaction of erection (*P*=0.0001) and percentage of full erection (*P*=0.0001). All three treatment groups showed significant improvement in positive mood scores (*P*=0.0001) and a decrease in negative mood scores (*P*=0.0001) without significant between-group differences. Minimal skin irritation at the application site was seen in 5.7 and 5.3% of patients in the testosterone gel 50 mg and 100 mg group. Minimal to severe skin irritation occurred in 65.8% of patients in the testosterone patch group. Mean serum PSA levels significantly increased with testosterone gel 100 mg (*P*=0.008) and testosterone gel 50 mg (*P*=0.05) with no significant increase in the testosterone patch group. As a group, both Hgb and Hct increased (*P*=0.0001) with statistical significance across treatment groups (*P*=0.0001). There were no overall treatment effects or intergroup differences in serum concentrations of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				total-C, HDL-C, LDL-C or TG (data not provided). Secondary: Not reported
Wang et al[24] Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 75 mg daily vs testosterone gel (AndroGel®) 100 mg daily	ES, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old, single morning serum testosterone level at screening of ≤10.4 nmol/L	N=163 36 months	Primary: Mean changes from baseline in serum testosterone, free testosterone, DHT, E2, SHBG, LH and FSH; mean changes from baseline in sexual function and mood, body composition, bone turnover markers, muscle strength and BMD; mean changes from baseline in Hgb, Hct, lipid profiles and blood chemistries; mean changes from baseline in serum PSA and prostate disease; safety Secondary: Not reported	Primary: Mean serum testosterone levels were significantly different (*P*=0.012) between dosing groups at baseline (six months of TRT). At 12 months, differences among the dosing groups became smaller but remained significant (*P*=0.042). Serum free testosterone levels followed the same pattern as testosterone. Mean serum DHT levels were different in the three dosing groups at 12 (*P*=0.0031) and 24 (*P*=0.018) months with the highest levels seen with testosterone gel 100 mg. Mean serum E_2 levels progressively increased from 6 to 24 months (*P*=0.0001) with significant differences between treatment groups. The highest levels of serum E_2 were seen with testosterone gel 100 mg. No significant change in SHBG was seen. Suppression of LH and FSH was maintained throughout with no significant changes after six months. The suppression was more pronounced with testosterone gel 100 mg. Significant improvements in sexual desire, enjoyment with or without a partner, percent full erection, and self-assessment of satisfaction with erections were maintained as a group throughout the study period. Positive mood scores were improved with treatment and were sustained (*P*=0.0022). Negative mood parameters were decreased and remained significantly lower (*P*=0.0013) than baseline without further changes after six months. Average total body mass increased by 1.2+0.3 kg at six months (*P*=0.0157) and did not significantly change with continued therapy. LBM increased significantly (*P*=0.0001) from baseline and remained increased throughout the study. A significant decrease in FM was seen at 30 months (*P*=0.088) without significant differences between doses.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Serum PTH levels significantly increased from baseline (*P*=0.0001) and continued to increase from six (*P*=0.0002) until 12 months when it remained stable throughout the rest of the treatment period. Serum SALP levels followed the same pattern (*P*=0.001). At 12 months serum osteocalcin was significantly elevated and remained elevated throughout treatment (*P*=0.0001). Serum procollagen levels transiently increased then steadily increased from six months to reach significant levels by 36 months (*P*=0.0001). Muscle strength increased but did not reach significance over time due to the large variation in patients. BMD of the hip (*P*=0.0004) and spine (*P*=0.0001) showed a gradual and progressive increase with treatment. No significant differences among treatment doses or older and younger patients were observed. Serum Hgb and Hct concentrations increased, compared with month zero (*P*=0.0001) and month six (*P*=0.001) and plateaued at 12 months. Small statistically significant increases in serum HDL-C levels (*P*<0.001), creatinine (*P*<0.001), and total bilirubin (*P*=0.001) were seen but were not clinically significant. No significant changes in total-C, LDL-C, serum liver enzymes, or other clinical chemistry parameters were observed. The mean serum PSA was 1.11+0.08 at six months and showed no further significant increases with continued treatment. Application-site reactions occurred in 12 of the 163 (7.4%) patients. Acne occurred in 12 (7.4%) of patients and gynecomastia was observed in eight more patients. Secondary: Not reported
Grober et al[25] AndroGel® 5 to 10 g	OL Hypogonadal	N=370 Treatment	Primary: Reasons for brand substitution, total and	Primary: Of the 370 hypogonadal men using testosterone gel, 20% underwent a brand substitution. The reasons for switching from AndroGel® to Testim®

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs Testim® 5 to 10 g	men on testosterone gel who underwent a brand substitution due to initial suboptimal biochemical or symptomatic response, mean age of men switched to Testim® was 60 years, mean age of men switched to AndroGel® was 52 years	duration after switch, 4 weeks	free testosterone, presence of hypogonadal symptoms Secondary: Not reported	(N=62) were poor efficacy (92%), hypertension (2%), skin reaction (2%), worsening symptoms (2%), and insurance coverage (2%). The reasons for switching from Testim® to AndroGel® (N=13) were scent (46%), poor efficacy (30%), fear of transfer to partner (8%), flushing (8%) and skin reaction (8%). Prior to substitution, patients initially treated with AndroGel®, had mean total and free testosterone levels of 311 ng/dL and 10.4 pg/mL, respectively. Total testosterone levels were <300 ng/dL in 58% of these patients. Following a change to Testim®, mean total and free testosterone levels increased to 484 ng/dL (*P*<0.001) and 14.6 pg/mL (*P*=0.01), respectively. Total testosterone levels remained <300 ng/dL in 17% of these patients. Among patients initially treated with Testim®, the mean total and free testosterone levels were 544 ng/dL and 18.0 pg/dL, respectively. Total testosterone levels were <300 ng/dL in 15% of men. Following a change to AndroGel®, mean total and free testosterone levels were 522 ng/dL (*P*=0.7) and 16.1 pg/mL (*P*=0.6), respectively. Total testosterone levels remained <300 ng/dL in 27% of these patients. Secondary: Not reported
Korbonits et al[26] Testosterone buccal 30 mg BID (Striant®) vs Andropatch®* or Androderm® TD patch 5 mg once daily	IT, MC, RCT Men with testosterone deficiency with a morning serum testosterone < 6.94 nmol/L, normal age-related PSA levels, and Hct < 50	N=66 7 days	Primary: Non-inferiority analysis (endpoints not defined) Secondary: Efficacy analysis of superiority (endpoints not defined)	Primary: Investigators concluded that non-inferiority was established (results not reported). Secondary: In the buccal testosterone group, the mean testosterone concentrations at all measured time points (days three, four, six, seven and eight) were within the physiological range; whereas mean concentrations at five time points were outside of the physiological range among patients in the testosterone patch group. For both mean (0 to24 hour) and minimum testosterone levels, the proportion of patients with levels outside the physiological range was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				lower in the buccal group than in the patch group (the differences; *P*<0.001 for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch (mean AUC ± SD; 451.31 ± 140.71 h*nmol/L vs. 304.63 ± 134.46 h*nmol/L; 95% CI, 1.25 to 1.91; *P* <0.00001). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group. Comparatively, the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group; however, the mean minimum 24-hour testosterone level was below the physiological range. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group. Testosterone concentrations were within the physiological range in the buccal group for a significantly greater portion of the 24-hour treatment period compared to the patch group (84.9 vs 54.9%; *P*<0.001). Mean DHT levels were within the normal range (1.03 to 2.92 nmol/L) for both the buccal group (2.36 ± 0.99 nmol/liter) and the patch group (1.2 ± 0.57 nmol/L). The median estradiol concentrations increased from baseline to day seven, but returned to baseline levels at the follow-up visit. The median increase from baseline to day seven was greater in the buccal group (55.07 pmol/liter) compared to the patch group (34.87 pmol/liter; *P*<0.001). A total of 51.5% of patients in the buccal group reported an adverse event compared to 47.1% in the patch group. The most commonly reported adverse events among both groups were application site disorders.
Wang et al[27]	OL with	N=155 OL	Primary:	Primary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Testosterone 60mg topical solution applied to each axilla once daily (Axiron®)	extension study Men ≥18 years with androgen deficiency (diagnosis of hypogonadism) and a BMI <35.0 kg/m^2 with testosterone levels on two consecutive samples < 10.4 nmol/L and a baseline Hgb level ≥ 110.5 g/L.	study 120 days N=71 extension study 60 days	Total testosterone and DHT (OL phase) Secondary: PDQ domain assessing sexual desire, enjoyment and performance, sexual activity, and mood, SF-36 health survey (extension phase)	At day 120, the proportion of patients completing the study with an average testosterone concentration (C_{avg}) in the normal range was 84.1%. Also, 76.1% and 84.8% of patients completed the study with a C_{avg} in the responder range on days 15/16 and 60/61, respectively. The mean serum testosterone level before and after dosing was within the adult male range over the 24-hour period on days 15, 60 and 120. The geometric mean of serum testosterone over 24 hours was 15.62 nmol/L (coefficient of variation [CV]; 38%). Among subjects who were responders at day 120, the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. Serum DHT levels and serum free testosterone remained relatively stable over the 24-hours following dosing. The mean day 15 baseline pre-dose DHT/T ratio was 0.23, and the mean DHT/T ratio remained between 0.17 to 0.26 throughout the 24-hour period. The ratio values among patients completing the study and among responders remained relatively constant from baseline. Secondary: Improvements in sexual desire and activity were apparent 15 days after application of testosterone and were sustained throughout the study. Statistically significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood as assessed by the PDQ domain for the seven days prior to visits one, 15, 60 and 120. Significant mean changes from day one to 120 for SF-36 Physical Component and SF-36 Mental Component scores were 1.55 (SD=7.72; *P*=0.0254) and 4.54 (SD=9.20; *P*<0.0001), respectively. Treatment-emergent adverse events occurring in >2% of patients receiving at least one dose of testosterone in the open-label study included: application site irritation, application site erythema, headache, increased hematocrit, nasopharyngitis, diarrhea, and vomiting. Three patients withdrew from the open-label phase of the study due to adverse events, including superficial thrombophlebitis, effects on lability/anger, and malignant melanoma; while two patients withdrew from the

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				extension phase of the study due to application site irritation and application site erythema.
Dobs et al[28] Testosterone gel 40 mg applied to the thighs once daily (Fortesta®) Dose adjustments allowed for a downward titration to a minimum of 10 mg daily and an upward titration to 70 mg daily.	MC, NC, OL Men 18 to 75 years, with primary or secondary hypo-gonadism (defined as a single serum testosterone concentration <250 ng/dL or two consecutive serum testosterone levels <300 ng/dL at least one week apart) and a BMI ≥22 kg/m^2 and <35 kg/m^2	N=149 90 days	Primary: The average serum total testosterone concentration over 24 hours (C_{avg} 0 to 24h) on Day 90 Secondary: The maximum serum testosterone concentration (C_{max}) on Day 90	Primary: Of the 129 patients with available data for analysis, the mean C_{avg} over 24 hours was 438.56 ± 162.51 ng/dL with 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal physiological range (≥300 and ≤1140 ng/dL) (95% CI, 70.3 to 84.7%). By day 35, 76.2% (95% CI, 68.8 to 83.6%) of patients had reached the primary endpoint. On day 90, 22.5% of patients had a total testosterone level <300 ng/dL. Secondary: The C_{max} ± SD was 827.6 ± 356.5 ng/dL on day 90. At endpoint, a total of 94.6% of patients achieved a C_{max} ≤1500 ng/dL, 1.6% of patients had levels between 1880 and 2500 ng/dL, and no patients had levels >2500 ng/dL. This C_{max} was evident by treatment day 35. Adverse events were reported in 46.3% of patients; however on 22.8% were considered related to the study medication. The most commonly reported adverse events were skin reactions, upper respiratory infections and sinusitis. Skin reactions were considered 'possibly' or 'probably' related to study medication in 16.1% of patients, of which 79.2% were mild in severity.
Kaufman et al[29] Testosterone 1.62% titrated to therapeutic dose vs testosterone 1.62% titrated to a specific serum testosterone level and then continued at dose for the remainder of the study	OL,ES Males 18 to 80 years of age with hypogonadism who completed a six month double blind study that elected to continue	N=191 182 days	Primary: Percentage of subjects achieving an average serum total testosterone concentration in the normal range of 300 to 1,000 ng/dL Secondary: Measurement of SHBG, LH, FSH, and selected serum	Primary: At the end of the study (day 364) 77.9% (95% CI, 70.0% to 84.6%) of subjects continuing on active testosterone treatment had Cav values within the normal range with 87.0% (95% CI, 66.4% to 97.2%) of the Formerly Placebo group reaching Cav values within in the normal range. A combined 79.2% (95% CI, 72.1% to 85.3%) of patients in both groups reached a Cav value within the normal range. Secondary: SHBG levels increased significantly from baseline on day 266 (P<0.0001) and on day 364 (P<0.0166) for the Continuing Active group but not for the Formerly Placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			inflammatory and cardiovascular risk markers, waist-to-hip ratio, and serum markers of bone metabolism; quality of life	LH levels decreased significantly from baseline on day 266 and day 364 with 1.62% testosterone treatment for the Continuing Active group (P<0.0001 for both days) and for the Formerly Placebo group (P<0.0054 and P<0.0309, respectively). FSH levels decreased significantly from baseline on day 266 and day 364 for the Continuing Active group (P<0.0001 for both days) and Formerly Placebo group (P<0.0001 and P<0.0087, respectively). Interleukin-10 decreased significantly from baseline on day 364 in the Continuing Active group (P<0.001) and on day 266 for the Formerly Placebo group (P<0.0089). MMP-9 levels decreased significantly from baseline for the Continuing Active group on both day 266 (P<0.0080) and day 364 (P<0.0055) but not for the Formerly Placebo group (P>0.05). Alkaline phosphatase values for bone-specific alkaline phosphatase significantly (P<0.0001) increased from baseline on day 266 for both groups, although no significant changes were seen on day 364. Values for type 1 cross-linked C-telopeptide decreased significantly from baseline on day 266 and day 364 for the Continuing Active group (P<0.001 both days) but not for the Formerly Placebo group (P > 0.05 both days). Scores on the SF-36 remained stable throughout the treatment period.
Miner et al[30] (abstract) Testosterone 1%	Cohort , PRO Men in the Testim Registry in the United States (TRiUS) – hypogonadal men who were prescribed TRT	N=849 12 months	Primary: Total testosterone, free testosterone, prostate specific antigen, sexual function, mood/depression, and cardiometabolic and anthropometric criteria	Primary: Mean total testosterone and free testosterone levels increased significantly after three months of therapy. For mean total testosterone level of 16.8 ± 9.87 nmol/L (P<0.001) and mean free testosterone level 286.3 ± 224.9 pmol/L (P<0.001). Mean PSA levels increased significantly (P=0.004) from 1.12 ± 1.11 µg/L at baseline to 1.26 ± 1.22 µg/L after 12 months of TRT, although changes were within guidelines (< 1.4 µg/L/year increase).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			before and after therapy Secondary: Not reported	Significant improvements were seen in sexual function and mood/depression at three months and in metabolic parameters at 12 months.
Blick et al (abstract)[31] Testosterone 1% in HIV/AIDS patients vs Testosterone 1% in non-HIV/AIDS patients	Cohort, PRO Men in the Testim Registry in the United States (TRiUS) – hypogonadal men who were prescribed TRT broken up by HIV status for this study	N=849 12 months	Primary: Total testosterone, free testosterone, sexual function, depression and body composition profiles Secondary: Not reported	Primary: During the 12 months, both the HIV/AIDS and non-HIV/AIDS cohorts experienced significant elevations in total testosterone and free testosterone levels to within normal ranges. Sexual function and depression scores improved and antidepressant medication use decreased in both cohorts. Body composition profiles improved significantly (P≤0.05) in men without HIV/AIDS and remained stable in men with HIV/AIDS during the 12 months of follow-up. Secondary: Not reported

*Agent not available in the United States.
Study abbreviations: AC=active-controlled, DB=double-blind, ES=extension study, IT=international, MA=meta-analysis, MC=multicenter, NC=non-comparative, OL=open-label, PC=placebo-controlled, PG=parallel-group, PK=pharmacokinetic, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, SA=single-arm
Miscellaneous abbreviations: AFS=American Fertility Society, BMD=bone mineral density, BMI=body mass index, C=cholesterol, C_{avg}=average concentration, DHT=dihydrotestosterone, E_2=Estradiol, FM=fat mass, FSH=follicle-stimulating hormone, Hct=hematocrit, HDL=high density lipoprotein, Hgb=hemoglobin, IIEF=International Index of Erectile Function-erectile function domain, IPSS= International Prostate Symptom Score, LBM=lean body mass, LDL=low density lipoprotein, LH=luteinizing hormone, PK=pharmacokinetics, PSA=prostate specific antigen, PTH=parathyroid hormone, SALP=bone-specific alkaline phosphatase, SHBG=sex hormone-binding globulin, T=testosterone, TG=triglycerides, TRT=testosterone replacement therapy

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Special Populations

Table 5. Special Populations[1-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Testosterone buccal mucoadhesive system	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone gel	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone implant pellet	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Indicated for the stimulation of puberty in selected males with clearly delayed puberty. No age is specified.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone patch	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma.	Use with caution, not studied in renal dysfunction. It appears that no dosage	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated	X	Contra-indicated

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in males <18 years have not been established.	adjustment is required.	with the development of severe hepatotoxicity		
Testosterone solution	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity	X	Contra-indicated

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Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Natesto®	Striant®	Testim®	Vogelxo®	Testopel®
Central Nervous System									
Abnormal dreams	-	-	-	1.3	-	-	-	-	-
Anxiety	-	-	a	-	-	-	-	-	a
Asthenia	-	<3	-	-	-	-	--	-	-
Depression	-	1	-	-	-	-	-	-	a
Dizziness	-	-	-	a	-	-	-	-	-
Emotional lability (including anger)	-	2.6 to 3	a	-	-	-	-	-	-
Headache	<4	<4	5 to 6	-	3.8	3.1	1	1	a
Insomnia			-	-	-	-	1	1	-
Libido, increased or decreased	-	<3	-	-	-	-	-	-	a
Migraine	-	-	-	a	-	-	-	-	-
Mood swings	-	-	-	-	-	-	1	1	-
Nervousness	-	-	a	-	-	-	-	-	-
Smell disorder	-	-	-	-	-	-	1	1	-
Dermatologic									
Acne	-	1 to 3	a	-	-	-	-	-	a
Allergic contact blistering	12	-	-	-	-	-	-	-	-
Alopecia	-	1	-	-	-	-	-	-	a
Application site burning	3	-	-	-	-	-	-	-	-
Application site erythema	<7	-	5 to 7	a	-		-	-	-
Application site edema	-	-	a	-	-	-	-	-	-
Application site exfoliation	<3	-	-	-	-	-	-	-	-
Application site induration	3	-	-	-	-	-	-	-	-
Application site reaction	-	3 to 5	-	-	-	-	2 to 4	4	-
Application site inflammation	-	-	-	-	-	-	-	-	a
Application site irritation	-	-	7 to 8	a	-	-	-	-	-
Application site pain	-	-	-	-	-	-	-	-	a

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Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Natesto®	Striant®	Testim®	Vogelxo®	Testopel®
Application site warmth	-	-	a	-	-	-	-	-	-
Application site vesicles	6	-	-	-	-	-	-	-	-
Contact dermatitis	-	2.1	-	a	-	-	-	-	-
Folliculitis	-	-	a	-	-	-	-	-	-
Pruritus	17 to 37	-	-	a	-	-	-	-	-
Rash	<3	-	-	a	-	-	-	-	-
Skin reactions	-	-	-	16.1	-	-	-	-	-
Endocrine and Urogenital									
Benign prostatic hyperplasia	-	-	-		-	-	1	-	-
Blood testosterone, increased	-	-	a	-	-	-	-	-	-
Blood testosterone, decreased	-	-	-	-	-	-	a	-	-
Breast pain	-	<3	-	-	-	-	-	-	-
Breast tenderness	-	-	a	-	-	-	-	-	-
Erectile dysfunction	-	-	-	a	-	-	-	-	-
Gynecomastia	-	<3	-	-	-	-	1	-	a
Hot flushes	-		-	-	-	-	1	1	-
Penile erections, excess frequency and duration	-	-	-	a	-	-	-	-	a
Penile erection, spontaneous	-	-	-	-	-	-	1	1	-
Polyuria	<3	-	-	-	-	-	-	-	-
Prostate abnormalities	5	-	-	-	-	-	-	-	-
Prostate disorder	-	3 to 5	-	-	-	-	-	-	-
Prostate enlarged	<3	-	-	-	-	-	-	-	-
Prostate specific antigen, increased	-	11.1	1 to 4	1.3	5.1	-	-	-	-
Testes disorder	-	<3	-	-	-	-	-	-	-
Urinary symptoms	-	<2	-	-	-	-	-	-	-
Gastrointestinal									

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Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Natesto®	Striant®	Testim®	Vogelxo®	Testopel®
Abdominal symptoms	-	-	-	a	-	-	-	-	-
Cholestatic jaundice	-	-	-	-	-	-	-	-	a
Diarrhea	<3	-	3 to 4	-	-	-	-	-	-
Gastrointestinal bleeding	<3	-	-	-	-	-	-	-	-
Gastroesophageal reflux disease	<3	-	-	-	-	-	-	-	-
Vomiting	-	-	3 to 4	-	-	-	-	-	-
Hematologic									
Bleeding	<3	-	-	-	-	-	-	-	-
Hematocrit/ hemoglobin increased	-	2.1	4 to 7	a	-	-	2	2	-
Polycythemia	-	-	-	a	-	-	-	-	-
Red blood cell count, elevation	-	-	a	-	-	-	-	-	-
Metabolic									
Blood glucose, increased	-	-	a	-	-	-	-	-	-
Cholesterol, increased	-	<2	-	-	-	-	-	-	-
Other									
Back pain	6	-	-	-	-	-	-	-	-
Blood pressure increase	-	<4	a	-	-	-	1	1	-
Bronchitis	-	-	-	-	3.8	-	-	-	-
Epistaxis	-	-	-	-	3.8	-	-	-	-
Fatigue	<3	-	-	a	-	-	-	-	-
Gum edema	-	-	-	-	-	2.0	-	-	-
Gum or mouth irritation	-	-	-	-	-	9.2	-	-	-
Gum pain	-	-	-	-	-	3.1	-	-	-
Gum tenderness	-	-	-	-	-	3.1	-	-	-
Influenza like illness/malaise	-	-	-	a	-	-	-	-	-
Laboratory test, abnormal	-	3 to 6	-	-	-	-	-	-	-
Lacrimation, increased	-	-	a	-	-	-	1	-	-
Nasal Discomfort	-	-	-	-	3.8	-	-	-	-

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Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Natesto®	Striant®	Testim®	Vogelxo®	Testopel®
Nasal Scab	-	-	-	-	3.8	-	-	-	-
Nasopharyngitis	-	-	a	-	3.8	-	-	-	-
Pain in extremities	-	-	-	a	-	-	-	-	-
Pelvic pain	<3	-	-	-	-	-	-	-	-
Rhinorrhea	-	-	-	-	3.8	-	-	-	-
Sinusitis	-	-	-	-	3.8	-	-	-	-
Taste sense, diminished	-	-	-	-	-	2.0	1	-	-
Taste bitter	-	-	-	-	-	4.1	-	-	-
Upper Urinary Tract Infection	-	-	-	-	3.8	-	-	-	-
Vitreous detachment	-	-	-	a	-	-	-	-	-

a Frequency of adverse event not reported.
- Incidence ≤1% or not reported.

Contraindications

Table 7. Contraindications[1-10]

Contraindications	Testosterone
Men with carcinoma of the breast or known or suspected carcinoma of the prostate	a
Women who are, or who may become pregnant, or who are breastfeeding.	a
Hypersensitivity to testosterone or any component of the product	a

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Precautions/Warnings

Table 8. Precautions/Warnings[1-10]

Warning/Precaution	Testosterone
Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer	a
Polycythemia	a
Venous Thromboembolism	a
Use in Women and Children	a (Androderm®)
Use in Women	a
Potential for Adverse Effects on Spermatogenesis	a
Hepatic Adverse Effects	a
Edema	a
Gynecomastia	a
Sleep Apnea	a
Lipids	a
Hypercalcemia	a
Decreased Thyroxine-Binding Globulin	a
Delayed puberty; use with caution	a (Testopel®)
Dosage adjustment less flexible	a (Testopel®)
Magnetic Resonance Imaging (MRI)	a (Androderm®)
Gum-related adverse reactions and limited long-term information on oral safety	a (Striant®)
Potential for Secondary Exposure to Testosterone	a (AndroGel®, Axiron®, Fortesta®, Testim®, Vogelxo®)
Flammability	a (AndroGel®, Axiron®, Fortesta®, Testim®, Vogelxo®)
Nasal Adverse Reactions	a (Natesto®)
Chronic nasal conditions, avoid use	a (Natesto®)

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Black Box Warnings Regarding Testosterone Solution and Gels (AndroGel®, Testim®, Axiron®, Vogelxo® & Fortesta®)[2-7]

WARNING
Secondary Exposure to Testosterone Virilization has been reported in children who were secondarily exposed to topical testosterone products. Children should avoid contact with any unwashed or unclothed application sites in men using testosterone gel/solution. Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

Drug Interactions

Table 7. Drug Interactions[1-10]

Drug	Interacting Medication	Potential Result
Testosterone	Anticoagulants	The concurrent administration of androgens with oral anticoagulants may decrease anticoagulant requirements.
Testosterone	Antidiabetic drugs (including insulin)	In diabetic patients, the metabolic effects of androgens may decrease blood glucose and insulin requirements.
Testosterone	oxyphenbutazone	Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
Testosterone	adrenocorticotropin & corticosteroids	Concurrent administration of androgens with adreno-corticotropin or corticosteroids may enhance edema formation.
Testosterone	propranolol	Administration of testosterone cypionate in a PK study led to an increased clearance of propranolol.
Testosterone patch	triamcinolone ointment	Pretreatment of the skin with triamcinolone ointment significantly reduced testosterone absorption from the patch drug delivery system.

PK=pharmacokinetic

Dosage and Administration

Table 8. Dosing and Administration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Testosterone buccal mucoadhesive system (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Striant® buccal system: Initial, maintenance: Apply one buccal system (30 mg) to the gum region twice daily in the morning and evening, 12 hours apart Application site: Striant®: Just above the incisor tooth (on either side of the mouth)	Safety and efficacy in males <18 years have not been established.	Buccal mucoadhesive system: Striant®: 30 mg
Testosterone gel (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired):	Safety and efficacy in males <18 years have not been established.	Metered dose pumps: AndroGel® 1%: 12.5 mg/actuation AndroGel® 1.62%:

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Generic Name	Adult Dose	Pediatric Dose	Availability
	Testim® 1% & AndroGel® 1% gel: Initial: 5 g applied once daily (preferably in the morning); Maintenance: 5 g to 10 g per day; Maximum: 10 g per day AndroGel® 1.62% gel: Initial: 40.5 mg applied once daily (preferably in the morning); Maintenance: 20.25 mg to 81 mg per day; Maximum: 10 g per day Fortesta® gel: Initial: 40 mg applied once daily (preferably in the morning); Maintenance: 10 mg to 70 mg per day; Maximum: 70 mg per day Vogelxo® gel Initial: 50 mg applied once daily (at that same time each day) Maintenance: 50 mg to 100 mg per day Maximum: 100 mg Recommended application sites: Testim®: shoulders and/or upper arms AndroGel 1%: shoulders and/or upper arms and/or abdomen AndroGel 1.62%: upper arms and/or shoulders Fortesta®: thighs Vogelxo®: shoulders and/or upper arms Natesto® Intranasal Gel: Initial, maintenance and maximum: two pump actuations (one per nostril) intranasally three times daily six to eight hours apart		20.25 mg/actuation Fortesta®: 10 mg/actuation Vogelxo® topical gel: 12.5 mg/actuation Unit-dose packets: AndroGel® 1%: 25 mg/pack 50 mg/pack AndroGel® 1.62%: 20.25 mg/pack 40.5 mg/pack Vogelxo® topical gel: 50 mg/pack Unit-dose tubes: Testim® 1%: 50 mg/tube Testosterone 1%: 50 mg/tube Vogelxo® topical gel: 50 mg/tube Intranasal Gel, metered-dose pump: Natesto: 5.5 mg/actuation
Testosterone implant pellet (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Testopel® implant pellet	Safety and efficacy in males <18 years have not been established.	Implant Pellet: Testopel® 75 mg

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Generic Name	Adult Dose	Pediatric Dose	Availability
	Initial, Maintenance: 150 to 450 mg (2 to 6 pellets) SQ every 3 to 6 months administered by a health care professional Delayed puberty in males: Generally dosing is in the lower range of that listed above and, for a limited duration (i.e. 4 to 6 months).		
Testosterone solution (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Axiron® solution Initial: 60 mg applied once daily to the axilla in the morning; Maintenance: 30 mg to 120 mg once daily; Maximum: 120 mg daily Application site: axilla	Safety and efficacy in males <18 years have not been established.	Meter Dose Pump: Axiron®: 30 mg/pump
testosterone transdermal system (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Androderm® patch: Initial: 4 mg/day patch applied once nightly; Maintenance: 2 mg/day to 6 mg/day applied at night Application site: back, abdomen, upper arms, or thighs	Safety and efficacy in males <18 years have not been established.	Transdermal system: Androderm®: 2 mg/day patch 4 mg/day patch

Clinical Guidelines

Table 9. Clinical Guidelines Using the Androgens

Clinical Guideline	Recommendations
The American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Evaluation and Treatment of**	· Testosterone replacement therapy (TRT) should maintain testosterone levels within the physiologic range (280 and 800 ng/dL). · TRT can be used in men with hypogonadism who are not interested in fertility or who are not able to achieve fertility. · Treatment of men with hypogonadism with TRT results in increased sexual interest and increased number of spontaneous erections. · Secondary sex characteristics (i.e., increased muscle mass, beard growth,

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Clinical Guideline	Recommendations
Hypogonadism in Adult Male Patients (2002)[14]	growth of pubic and axillary hair, and phallus growth) improve with TRT. · In adolescent male patients with hypogonadotropic hypogonadism, TRT increases bone mineral density in comparison with that in male patients with hypogonadism not receiving TRT. In prepubertal-onset hypogonadotropic hypogonadism, diminished bone mass may be only marginally improved by TRT. · No specific recommendations can be made on the possible normalization of growth hormone levels in elderly men with TRT. Further research is needed to clarify the potential risks and benefits associated with therapy. · Whether TRT in men with hypogonadism increases, decreases, or has a neutral effect on cardiovascular risk remains uncertain. · Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available in the Unites States are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects, such as hemorrhagic liver cysts, cholestasis, and hepatocellular adenoma.
The Endocrine Society: **Clinical Practice Guidelines: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes (2010)**[15]	· TRT is recommended for symptomatic men with classical androgen deficiency syndromes to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. · TRT is not recommended for use in patients with breast or prostate cancer. · TRT is not recommended without further urological evaluation in patients with palpable prostate nodule or induration or a prostate specific antigen (PSA) 4 ng/mL or PSA 3 ng/mL in men at high risk of prostate cancer (i.e., African Americans or men with first degree relatives with prostate cancer). · TRT is not recommended in patients with a hematocrit >50%, untreated severe sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure or in those desiring fertility). · Initiating TRT is recommended with any of the following regimens after evaluating patient preference, consideration of pharmacokinetics, treatment burden, cost: o Testosterone enanthate or cypionate: 75 to 100 mg IM weekly; or 150 to 200 mg IM every two weeks. o Testosterone patches: one or two 5-mg non-genital patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas. o Testosterone 1% gel: 5 to 10 g applied daily over a covered area of non-genital skin (patients should wash hands after application). o Testosterone buccal: apply one 30 mg tablet to buccal mucosa every 12 hours. o Testosterone pellets implanted subcutaneously at intervals of 3 to 6 months; the dose and regimen vary with the formulation used. o Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets where available. (Note: testosterone undecanoate is not available in the United States.) · Monitoring is advised three to six months after treatment initiation and then annually to assess symptom response, the presence of any adverse effects, and to check compliance. · Recommendations aim at achieving serum testosterone levels during treatment in the mid-normal range. In men receiving testosterone enanthate or cypionate, aiming for testosterone levels between 400 and 700 ng/dL one week after the injection is recommended.

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Clinical Guideline	Recommendations
	· Hematocrit monitoring is advised at baseline, at three to six months, then annually; if exceeds 54% therapy should be discontinued until reduced to a safe level. · Bone mineral density testing of the lumbar spine, femoral neck, and hip after one to two years of testosterone therapy is advised in hypogonadal men with osteoporosis or low trauma fracture. · Digital rectal exam is advised in men ≥ 40 years with a baseline PSA > 0.6 ng/mL, prior to initiating therapy, at three to six months, and then based upon evidence-based guideline recommendations. · Urological consultation is advised if there is an increase in serum or plasma PSA > 1.4 ng/mL within any 12-month period of testosterone treatment; a PSA velocity of more than 0.4 ng/mL·yr using the PSA level after six months of testosterone administration as the reference (PSA velocity should be used only if there are longitudinal PSA data for more than two years); detection of a prostatic abnormality on digital rectal examination; or a AUA/IPSS score >19. · TRT should be offered to men with low testosterone levels and low libido to improve libido and to men with erectile dysfunction (ED) who have low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED. · TRT should not be offered to all older men with a low testosterone level. · Clinicians should consider offering TRT on an individualized basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency. · Short-term TRT may be considered as adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass and muscle strength. · Short-term TRT may be offered to men receiving high dose glucocorticoids who have low testosterone levels to promote preservation of lean body mass and bone mineral density.
International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), American Society of Andrology (ASA): **ISA, ISSAM, EAU, EAA, and ASA Recommendations: Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males (2009)**[16]	· Late-onset hypogonadism is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range). This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems. · Response to TRT should be assessed. If there is no improvement of signs symptoms within a reasonable time interval (three to six months is adequate for libido and sexual function, muscle function, and improved body fat; a longer interval is required to see improvement in bone mineral density), TRT should be withdrawn. Further investigation for other causes of symptoms is then mandatory. · TRT improves body composition (i.e., decrease of fat mass, increase of lean body mass) in men with hypogonadal values of testosterone. Secondary benefits of these changes of body composition on strength, muscle function, metabolic, and cardiovascular dysfunction are suggested by available data but require confirmation by large-scale studies. · Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal younger and older men. Bone density in hypogonadal men of all ages increases under TRT. Fracture data are not yet available and thus the long-term benefit of TRT requires further investigation. · Men with erectile dysfunction (ED) and/or diminished libido and documented testosterone deficiency are candidates for TRT. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short (i.e., three months) therapeutic trial may

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Clinical Guideline	Recommendations
	be justified. An absence of response calls for discontinuation of TRT. There is evidence suggesting therapeutic synergism with combined use of TRT and phosphodiesterase-5 (PDE5) inhibitors in hypogonadal or borderline eugonadal men; however, these observations require additional study. The combination treatment should be considered in hypogonadal patients with ED failing to respond to either treatment alone. It is unclear whether men with hypogonadism and ED should be treated initially with testosterone, PDE5 inhibitors, or the combination. · Currently available intramuscular (IM), 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. · Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism because of the possible development of an adverse event that may require rapid discontinuation of TRT. · Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, mid-to-lower young adult male serum testosterone levels seem appropriate as the therapeutic goal. Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels. · The 17-α-alkylated androgen preparations such as methyltestosterone are obsolete because of their potential liver toxicity and should no longer be prescribed. · Due to insufficient data regarding the therapeutic and adverse effects of human chorionic gonadotropin treatment in older men and its higher cost, the treatment cannot be recommended in late-onset hypogonadism except when fertility is an issue. Antiestrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels. Adequate evidence does not exist to recommend their use. · TRT is contraindicated in men with prostate or breast cancer. TRT is relatively contraindicated in men at high risk of developing prostate cancer. It is unclear whether localized low-grade prostate cancer represents a relative or absolute contraindication for treatment. · Men with significant erythrocytosis, untreated obstructive sleep apnea, and untreated severe congestive heart failure should not be started on TRT without prior resolution of the comorbid condition. · Age is not a contraindication to initiate TRT. Individual assessment of comorbidities (as possible causes of symptoms) and potential risks versus benefits of TRT is particularly important in elderly men.
American College of Physicians: **Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction (2009)**[17]	· Treatment with a phosphodiesterase type 5 (PDE5) inhibitor should be initiated in men who seek treatment for erectile dysfunction and who do not have a contraindication to therapy. · The clinical benefit associated with the use of PDE5 inhibitors was demonstrated regardless of the cause (such as diabetes, depression, or prostate cancer) or baseline severity of erectile dysfunction. · Improvement in erectile functioning was related to higher doses for sildenafil and vardenafil but not for tadalafil; however, higher doses were associated with a greater risk for adverse events. · There is insufficient evidence to compare the efficacy and adverse events of the different PDE5 inhibitor agents.

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Clinical Guideline	Recommendations
	· The choice of which PDE5 inhibitor to administer should be made based on the individual preferences of men with erectile dysfunction, including the ease of use, cost, and tolerability. · Due to inconclusive evidence, there are no recommendations against or for routine use of hormonal blood tests or hormonal treatment (i.e., testosterone oral, injection, gel, patch, and cream) in the management of erectile dysfunction. · Clinicians should individualize decisions to measure hormone levels on the basis of clinical presentation and physical findings that suggest hormonal abnormality. · There is insufficient evidence to determine whether PDE5 inhibitors are associated with an increased risk for non-arteritic anterior ischemic optic neuropathy.

Conclusions

The testosterone products included in this review are Androderm®, AndroGel®, Axiron®, Fortesta®, Natesto®, Striant®, Testim®, Testopel® and Vogelxo®. These agents primarily differ in their formulations and site of administration. Different formulations include the topical gels, solutions and transdermal patches in addition to a nasal gel, mucoadhesive buccal tablet and an implantable pellet. Currently, only AndroGel® has an A-rated generic formulation. All of the products are indicated for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with Testopel® (testosterone) implantable pellets also having an indication to stimulate puberty in certain carefully selected males with clearly delayed puberty.[1-10]

Available head-to-head studies suggest that Testim® and AndroGel® may produce higher serum testosterone concentrations, and reduce body fat more so compared to Androdem.[20-23] One study suggests that patients with a suboptimal response to AndroGel® may experience symptomatic improvements in libido, erectile function and energy levels following a switch to Testim®.[24] No studies are available that evaluate Natesto®, Axiron® or Fortesta® compared to other androgens or topical testosterone products. The results from a meta-analysis demonstrated that the transdermal patch showed the greatest rate of erectile response compared to the (intramuscular) IM and oral formulations of testosterone, with the IM and oral products showing essentially equivalent response rates.[32]

According to current consensus guidelines, IM and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects.[14,16] The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. Furthermore, currently available guidelines do not give preference to one topical preparation versus another.

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