Therapeutic Class Overview
Topical Androgens

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).[1-6] 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® and Testim® 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. Androderm® is applied at night, while the others are generally applied in the morning.[1-6] 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 topical testosterone product labeling includes 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. 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.[1-6] There are no topical testosterone products available generically.

  Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.[7-11] 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.[11] 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.[11] 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.[9] 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.[7-11]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

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 hypogonadotropic hypogonadism in males (congenital or acquired)	AndroGel® 1%: Metered-dose pump (60 actuations per container; 12.5 mg testosterone per actuation in 1.25 g gel) Packet (30 packets per carton; 25 mg testosterone in 2.5 g gel or 50 mg testosterone in 5 g gel)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		AndroGel® 1.62%: Metered-dose pump (60 actuations per container; 20.25 mg testosterone per actuation in 1.25 g gel) Packet (30 packets per carton; 20.25 mg testosterone in 1.25 g gel or 40.5 mg testosterone in 2.5 g gel)	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump (60 actuations per container; 30 mg testosterone per actuation in 1.5 mL of solution)	-
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump (60 actuations per container; 10 mg testosterone per actuation in 0.5 g gel)	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes (30 tubes per carton; 50 mg testosterone in 5 g gel)	-

Evidence-based Medicine

- In one study comparing Testim® 50 and 100 mg, Androderm® and placebo, all treatments significantly increased serum testosterone and dihydrotestosterone (DHT) levels. All treatments increased lean body mass (LBM); however, the Testim® 100 mg group increased LBM significantly more compared to the Androderm® and placebo groups (P<0.05 for all). Testim® and Androderm® significantly decreased fat mass compared to placebo. Only Testim® 100 mg produced significant improvements in sexual function. There were no significant differences among groups with regard to improving mood.[12]
- Compared to Androderm®, AndroGel® 100 mg significantly increased levels of testosterone and free testosterone compared to AndroGel® 50 mg and Androderm®. 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 greater with Androderm®.[13]
- In a study comparing AndroGel® and Androderm®, the average serum testosterone levels increased most with AndroGel® 100 mg (P values not reported). 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 experienced significant improvements in sexual function. AndroGel® treatment significantly increased prostate specific antigen levels. Skin irritation at the application site was more frequent in the Androderm® group compared to AndroGel® 100 mg and 50 mg groups.[14]
- The results from a study by Grober et al demonstrated the efficacy of changing from one testosterone gel preparation to another after suboptimal response (N=370). Among men switching from AndroGel® to Testim®, 69, 58 and 65% experienced improvements in libido, erectile function and energy levels, respectively. The rates of improvement for these parameters for men switching from Testim® to AndroGel® were 46, 39 and 46%, respectively.[15]
- 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.[16] 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®.[17]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.[8-10,18]
  - 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.[8,10]
  - 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.[8,10]
  - 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.[8-10]

- Other Key Facts:
  - There are no generic topical testosterone products available.

References

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Therapeutic Class Review
Topical Androgens

Overview/Summary

Testosterone products are available in various formulations including oral administration, intramuscular injection, topical gel, transdermal patch, topical solution, implantable pellets administered by the subcutaneous route and a buccal delivery system. This review will focus on the topically administered testosterone products listed in Table 1. All of these products are approved by the Food and Drug Administration (FDA) as testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).[1-5] 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 transdermal patch. AndroGel®, Fortesta® and Testim® are available in gel preparations and Axiron® is formulated as a topical solution. These products are available as metered-dose pumps and single-use packets/tubes and are applied once daily. The Androderm® patch is applied at night, while the other products are generally applied in the morning. A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, hydrocortisone cream may be applied after patch has been removed to reduce skin irritation.[1-6] No topical testosterone products are available generically.

Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad (testes) function.[7-12] 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.[12] 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.[12] 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.[10] 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.[10] 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.[8,12]

Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.[7-11] Oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes and hepatic adverse events; however, they 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 considering patient preferences, pharmacokinetic profiles of the agents, treatment burden and cost. 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 therapy. Moreover, the guidelines do not recommend one topical preparation over another. Several clinical studies have demonstrated that topically applied testosterone restores serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, muscle development and improves bone mineral density in hypogonadal men. The results of three head-to-head trials favored the use of the gel over the patch.[14-17]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Testosterone (Androderm®, AndroGel®, Axiron®, Fortesta®, Testim®)	Androgens	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-5]

Indication	Testosterone (Androderm®, AndroGel®, Axiron®, Fortesta®, Testim®)
Hypogonadism in males, primary (congenital or acquired)	✔ (all)
Hypogonadotropic hypogonadism in males (congenital or acquired)	✔ (all)

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.[6] Testosterone replacement therapy is not indicated for the treatment of erectile dysfunction in men with normal serum testosterone concentrations.

Pharmacokinetics

Table 3. Pharmacokinetics[1-7]

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

DHT=dihydrotestosterone.
* The half-life not reported for all products but range of 10 to 100 minutes referenced.
† The parameters are reported for the respective delivery systems as available in the prescribing information.
‡ Based on intramuscular administration.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the topical testosterone products in their Food and Drug Administration-approved indications are described in Table 4.[14-22]

In a randomized, 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) compared to the transdermal system. All three treatments significantly increased lean body mass (LBM), while only Testim® 100 mg significantly decreased percentage of fat. Significant differences between treatment groups were observed in the alleviation of negative mood and improvements in spontaneous erections favoring Testim® over transdermal testosterone. All three treatment groups experienced 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.[14] In a second study comparing two doses of Testim®, a transdermal testosterone patch (Androderm®) and placebo, all treatment groups achieved similar increases in serum testosterone and DHT levels. All treatment groups experienced increases in LBM; however, the Testim® 100 mg group experienced a significantly greater increase in LBM compared to the Androderm® and placebo groups ($P<0.05$ for each). The use of both Testim® and Androderm® resulted in significant decreases in fat mass compared to placebo. Only Testim® 100 mg significantly improved sexual

function compared to placebo. There were no significant differences among treatment groups in improving mood. Androderm® was associated with more treatment-emergent adverse events compared to the other treatment groups.[15]

When two doses of a testosterone gel (AndroGel®) were compared to Androderm®, AndroGel® 100 mg was associated with significantly higher levels of serum testosterone and free testosterone compared to AndroGel® 50 mg and Androderm®. 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 greater in the Androderm® group.[16] In a study by Wang et al comparing AndroGel® and Androderm®, average serum testosterone levels were increased greatest with AndroGel® 100 mg (*P* values not reported). A decrease in percent body fat and total fat mass occurred in all treatment groups; however, this was only significant in the AndroGel® treatment group. All treatment groups experienced 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.[17]

In an extension study, patients treated with three doses of AndroGel® were observed for a period of 36 months. 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 observed. Serum levels of prostate specific antigen showed no further significant increases past six months of treatment. Treatment-emergent adverse events included application site reactions, acne and gynecomastia.[18]

Grober et al evaluated the efficacy of changing from one testosterone gel preparation to another after suboptimal response. 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).[19]

In a multicenter, randomized controlled 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. 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 (zero to 24 hour) and minimum testosterone levels ($P<0.001$ 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.[20]

In an open-label efficacy trial (N=155), Wang et al evaluated varying doses of testosterone 2% topical solution (Axiron®) applied to the axilla once daily. During the open-label phase of the trial, the mean serum

testosterone level before and after application of the testosterone solution was within the adult male range over the 24-hour measurement period on days 15, 60 and 120. Among subjects who were responders at study endpoint (120 days), the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. In addition, the proportion of patients completing the study with an average testosterone concentration (C_{avg}) in the normal range was 76.1% on day 15/16, 84.8% on day 60/61, and 84.1% at day 120. Serum DHT levels and serum free testosterone remained relatively stable over the 24 hours following dosing. The DHT/testosterone ratio values among patients completing the study and among responders remained relatively constant from baseline. Improvements in sexual desire and activity were apparent 15 days after application of testosterone solution 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 Psychosexual Daily Questionnaire domain for the seven days prior to visits one, 15, 60 and 120. Mean changes from day 1 to 120 in the SF-36 Physical Component and SF-36 Mental Component scores were also statistically significant. Treatment-emergent adverse events in the open-label study included application site irritation, application site erythema, headache, increased hematocrit, nasopharyngitis, diarrhea and vomiting.[21]

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. At study endpoint (90 days), the mean serum total testosterone concentration over 24 hours (C_{avg} zero 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 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.[22]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Hypogonadism				
McNicholas et al[14] 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) compared to 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 significantly greater compared to 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 compared to testosterone patch at 90 days (*P*<0.001). Results at 30 and 60 days were consistent with those observed 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. 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[15] 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 two patches daily in the morning vs placebo	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. Patients treated with testosterone gel 100 mg had a significant increase in mean changes in testosterone concentrations compared to patients treated with the testosterone patch (P<0.001). The testosterone gel 50 mg and 100 mg groups experienced a 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 observed across treatment groups. At 90 days, the mean change in LBM was 1.5±4.5, 1.7±2.6, 0.9±1.8 and 0.6±1.8 kg for patients receiving testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch and placebo, respectively. Increases in LBM were significantly higher with testosterone gel 100 mg compared to the testosterone patch and placebo (P<0.05 for each comparison). With the exception of placebo treatment, all treatments resulted in a significant decrease in FM compared to placebo (P<0.01). At 90 days, testosterone gel 100 mg treatment was associated with significant improvements in spontaneous erections (P<0.001), sexual motivation (P<0.05), sexual desire (P<0.01) and sexual performance (P<0.05) compared to placebo. 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[16] Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg two 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	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 zero, one, 30, 90 and 180 days; serum DHT, E_2, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days; safety Secondary: Not reported	Primary: At 30 and 90 days, testosterone gel 100 mg produced significantly higher C_{avg} testosterone levels compared to testosterone 50 mg and testosterone patch (27.46±1.12 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 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). 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 compared to the testosterone patch (*P*=0.0001). Mean serum increases to stable levels of E_2 occurred in 9.2,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
instructed to apply AndroGel® 75 mg once daily for days 91 through 180.				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 demonstrated 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[17] Testosterone gel (AndroGel®) 50 mg daily vs 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	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: Mean change from baseline in serum testosterone concentrations, body composition, and 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	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 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 observed in all three treatment groups without intergroup differences at 90 and 180 days. All subjects experienced significant improvements 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 had significant improvements

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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.			90 days; mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries Secondary: Not reported	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 observed in 5.7 and 5.3% of patients receiving testosterone gel 50 mg and 100 mg, respectively. 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 total-C, HDL-C, LDL-C or TG (data not provided). Secondary: Not reported
Wang et al[18] 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	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 significantly 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 six 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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	partner, percent full erection, and self-assessment of satisfaction with erections were maintained as a group throughout the study period. Positive mood scores were significantly 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. The 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. 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. The 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 toto 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 163 (7.4%) patients. Acne occurred in 12 of patients and gynecomastia was observed in eight more patients. Secondary: Not reported
Grober et al[19] Testosterone gel (AndroGel®) 5 to 10 g vs testosterone gel (Testim®) 5 to 10 g	OL Hypogonadal 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	N=370 Treatment duration after switch, 4 weeks	Primary: Reasons for brand substitution, total and free testosterone, presence of hypogonadal symptoms Secondary: Not reported	Primary: Twenty percent of the 370 hypogonadal men using testosterone gel underwent a brand substitution. The reasons for switching from AndroGel® to Testim® (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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Korbonits et al[20] Testosterone buccal (Striant®) 30 mg BID vs testosterone patch (Andropatch®* or Androderm®) 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 (zero to 24 hour) and minimum testosterone levels, the proportion of patients with levels outside the physiological range was lower in the buccal group than in the patch group (*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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 compared to the patch group (55.07 vs 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[21] Testosterone topical solution (Axiron®) 60 mg applied to each axilla once daily	OL with ES Men ≥18 years with androgen deficiency (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.	N=155 OL study 120 days N=71 extension study 60 days	Primary: Total testosterone and DHT (OL phase) Secondary: PDQ domain assessing sexual desire, enjoyment and performance, sexual activity, and mood, SF-36 health survey (ES)	Primary: 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 (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 15 day baseline pre-dose DHT/testosterone ratio was 0.23, and the mean DHT/testosterone 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Treatment-emergent adverse events occurring in >2% of patients receiving at least one dose of testosterone in the OL study included application site irritation, application site erythema, headache, increased hematocrit, nasopharyngitis, diarrhea, and vomiting. Three patients withdrew from the OL phase of the study due to adverse events, including superficial thrombophlebitis, effects on lability/anger, and malignant melanoma. Two patients withdrew from the ES of the study due to application site irritation and application site erythema.
Dobs et al[22] Testosterone gel (Fortesta®) 40 mg applied to the thighs once daily 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} zero 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.

*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, RCT=randomized controlled trial
Miscellaneous abbreviations: AUC=area under the curve, BMD=bone mineral density, BMI=body mass index, C=cholesterol, C_{avg}=average concentration, CV=coefficient of variation, DHT=dihydrotestosterone, E_2=Estradiol, FM=fat mass, FSH=follicle-stimulating hormone, Hct=hematocrit, HDL=high density lipoprotein, Hgb=hemoglobin, LBM=lean body mass, LDL=low density lipoprotein, LH=luteinizing hormone, PDQ=psychosexual daily questionnaire, PK=pharmacokinetics, PSA=prostate specific antigen, PTH=parathyroid hormone, SALP=bone-specific alkaline phosphatase, SD=standard deviation, SHBG=sex hormone-binding globulin, SF-36=short form 36 questions, TG=triglycerides, TRT=testosterone replacement therapy

Special Populations

Table 5. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Testosterone gel	No dosage adjustment is required in the elderly. Safety and efficacy in males <18 years have not been established. Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X .	Contra-indicated
Testosterone patch	No dosage adjustment is required in the elderly. Safety and efficacy in males <18 years have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Contra-indicated
Testosterone solution	No dosage adjustment is required in the elderly. Safety and efficacy in males <18 years have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Contra-indicated

Adverse Drug Events

Table 6 outlines the most frequently reported adverse events for topical testosterone. In general, all topical testosterone agents share the same safety concerns; however, the transdermal patch is associated with a higher incidence of application-site reactions compared to other topical formulations.

Table 6. Adverse Drug Events (%)[1-5]

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
Central Nervous System					
Abnormal dreams	-	-	-	1.3	-
Anxiety	-	-	✔	-	-
Asthenia	-	<3	-	-	-
Depression	-	1	-	-	-
Dizziness	-	-	-	✔	-
Emotional lability (including anger)	-	2.6 to 3	✔	-	-
Headache	<4	<4	5 to 6	-	1
Insomnia	-	-	-	-	1
Libido, increased or decreased	-	<3	-	-	-
Migraine	-	-	-	✔	-
Mood swings	-	-	-	-	1
Nervousness	-	-	✔	-	-
Smell disorder	-	-	-	-	1

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
Dermatologic					
Acne	-	1 to 3	✔	-	-
Allergic contact blistering	12	-	-	-	-
Alopecia	-	1	-	-	-
Application site burning	3	-	-	-	-
Application site edema	-	-	✔	-	-
Application site erythema	<7	-	5 to 7	✔	-
Application site exfoliation	<3	-	-	-	-
Application site induration	3	-	-	-	-
Application site irritation	-	-	7 to 8	✔	-
Application site reaction	-	3 to 5	-	-	2 to 4
Application site vesicles	6	-	-	-	-
Application site warmth	-	-	✔	-	-
Contact dermatitis	-	2.1	-	✔	-
Folliculitis	-	-	✔	-	-
Pruritus	17 to 37	-	-	✔	-
Rash	<3	-	-	✔	-
Skin reactions	-	-	-	16.1	-
Endocrine and Urogenital					
Benign prostatic hyperplasia	-	-	-	-	1
Blood testosterone, increased	-	-	✔	-	-
Blood testosterone, decreased	-	-	-	-	✔
Breast pain	-	<3	-	-	-
Breast tenderness	-	-	✔	-	-
Erectile dysfunction	-	-	-	✔	-
Gynecomastia	-	<3	-	-	1
Hot flushes	-	-	-	-	1
Penile erections, excess frequency and duration	-	-	-	✔	-
Penile erection, spontaneous	-	-	-	-	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	-
Testes disorder	-	<3	-	-	-
Urinary symptoms	-	<2	-	-	-
Gastrointestinal					
Abdominal symptoms	-	-	-	✔	-
Diarrhea	<3	-	3 to 4	-	-
Gastrointestinal bleeding	<3	-	-	-	-
Gastroesophageal reflux disease	<3	-	-	-	-
Vomiting	-	-	3 to 4	-	-
Hematologic					
Bleeding	<3	-	-	-	-

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
Hematocrit/ hemoglobin increased	-	2.1	4 to 7	✔	2
Polycythemia	-	-	-	✔	-
Red blood cell count, elevation	-	-	✔	-	-
Metabolic					
Blood glucose, increased	-	-	✔	-	-
Cholesterol, increased	-	<2	-	-	-
Other					
Back pain	6	-	-	-	-
Blood pressure increase	-	<4	✔	-	1
Fatigue	<3	-	-	✔	-
Influenza like illness/malaise	-	-	-	✔	-
Laboratory test, abnormal	-	3 to 6	-	-	-
Lacrimation, increased	-	-	✔	-	1
Nasopharyngitis	-	-	✔	-	-
Pain in extremities	-	-	-	✔	-
Pelvic pain	<3	-	-	-	-
Taste sense, diminished	-	-	-	-	1
Vitreous detachment	-	-	-	✔	-

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

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
Men with carcinoma of the breast or known or suspected carcinoma of the prostate	✔	✔	✔	✔	✔
Women who are, or who may become pregnant, or who are breastfeeding	✔	✔	✔	✔	✔

Black Box Warnings Regarding Testosterone (AndroGel®, Axiron®, Fortesta® and Testim®)[2-5]

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.

Warnings/Precautions

Table 8. Warnings and Precautions[1-5]

Warning/Precaution	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
Worsening of benign	✔	✔	✔	✔	✔

Warning/Precaution	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
prostatic hyperplasia; monitor patients for worsening symptoms					
Prostate cancer risk; evaluate patients prior to treatment and three to six months following initiation of treatment	✔	✔	✔	✔	✔
Polycythemia; increases in hematocrit, reflective of increases in red blood cell mass, may dose modification	✔	✔	✔	✔	✔
Spermatogenesis; may be suppressed by large doses of exogenous androgens and may lead to adverse effects on semen parameters	✔	✔	✔	✔	✔
Hepatic effects; prolonged use of high doses of orally active 17-alpha-alkyl androgens has been associated with serious hepatic adverse effects	✔	✔	✔	✔	✔
Edema; androgens may promote sodium and water retention, resulting in complications in patients with pre-existing cardiac, renal or hepatic disease	✔	✔	✔	✔	✔
Gynecomastia; potential development in patients treated with androgens	✔	✔	✔	✔	✔
Sleep apnea; androgens may potentiate sleep apnea in some patients, especially those with obesity and chronic lung disease	✔	✔	✔	✔	✔
Lipids; changes in serum lipids may require dose adjustment or discontinuation of therapy	✔	✔	✔	✔	-
Hypercalcemia; use with caution in cancer patients at risk of hypercalcemia	✔	✔	✔	✔	-
Decreased thyroxine-binding globulin; may result in decreased total T4 serum concentration and increased uptake of T3 and T4	✔	✔	✔	✔	-
Magnetic resonance	✔	-	-	-	-

Warning/Precaution	Androderm®	AndroGel®	Axiron®	Fortesta®	Testim®
imaging; skin burns have been reported at the application site in patients wearing an aluminized transdermal system during a magnetic resonance imaging scan					
Potential secondary exposure; cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance	-	✔	✔	✔	✔
Flammability; alcohol based products are flammable	-	✔	✔	✔	✔

Drug Interactions

Table 9. Drug Interactions[1-5]

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	Adrenocorticotropin & corticosteroids	Concurrent administration of androgens with adrenocorticotropin or corticosteroids may enhance edema formation.
Testosterone	Oxyphenbutazone	Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
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[1-6]

Testosterone products are controlled substances under the Anabolic Steroid Control Act and have all been assigned as Schedule III products.

Table 10. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Testosterone gel (CIII)	Hypogonadism in males, primary (congenital or acquired), hypogonadotropic hypogonadism in males (congenital or acquired): AndroGel® 1% gel: initial, 50 mg (four pump actuations, two 25 mg packets or one 50 mg packet) applied once daily in the morning to the shoulders, upper arms or	Safety and efficacy in males <18 years have not been established.	AndroGel® 1%: Metered-dose pump (60 actuations per container; 12.5 mg testosterone per actuation in 1.25 g gel) Packet (30 packets per carton; 25 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	abdomen area; maintenance, 50 mg to 100 mg applied once daily in the morning to the shoulders, upper arms or abdomen area AndroGel® 1.62% gel: initial, 40.5 mg (two pump actuations or one 40.5 mg packet) applied once daily in the morning to shoulders and upper arms; maintenance, 20.25 mg to 81 mg applied once daily in the morning to shoulders and upper arms; maximum, 81 mg applied once daily in the morning to shoulders and upper arms Fortesta® gel: initial, 40 mg (four pump actuations) applied once daily in the morning to thighs; maintenance, 10 mg to 70 mg applied once daily in the morning to thighs; maximum, 70 mg applied once daily in the morning to thighs Testim® 1% gel: initial, 50 mg (one tube) applied once daily in the morning to shoulders and/or upper arms; maintenance, 5 mg to 10 mg applied once daily in the morning to shoulders and/or upper arms; maximum, 10 mg applied once daily in the morning applied to shoulders and/or upper arms		testosterone in 2.5 g gel or 50 mg testosterone in 5 g gel) AndroGel® 1.62%: Metered-dose pump (60 actuations per container; 20.25 mg testosterone per actuation in 1.25 g gel) Packet (30 packets per carton; 20.25 mg testosterone in 1.25 g gel or 40.5 mg testosterone in 2.5 g gel) Fortesta®: Metered-dose pump (60 actuations per container; 10 mg testosterone per actuation in 0.5 g gel) Testim® 1%: Unit-dose tubes (30 tubes per carton; 50 mg testosterone in 5 g gel)
Testosterone solution (CIII)	Hypogonadism in males, primary (congenital or acquired), hypogonadotropic hypogonadism in males (congenital or acquired): Topical solution: initial, 60 mg (two pump actuations) applied once daily to axilla; maintenance, 60 mg to 120 mg applied once daily to axilla; maximum, 120 mg applied once daily to axilla	Safety and efficacy in males <18 years have not been established.	Axiron®: Metered-dose pump (60 actuations per container; 30 mg testosterone per actuation in 1.5 mL of solution)
Testosterone transdermal system (CIII)	Hypogonadism in males, primary (congenital or acquired), hypogonadotropic hypogonadism in males (congenital or acquired): Transdermal system: initial, 4 mg/day applied once nightly to back, abdomen, upper arms, or thighs; maintenance, 2 to 6 mg/day applied once nightly to back, abdomen, upper arms, or thighs	Safety and efficacy in males <18 years have not been established.	Androderm®: 2 mg/day patch 4 mg/day patch

Clinical Guidelines

Table 11. Clinical Guidelines Using the Androgens

Clinical Guideline	Recommendations
European Association of Urology: **Guidelines on Male Hypogonadism (2012)**[7]	• The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism. • Total testosterone assessment should be repeated at least on two occasions in men with: o Total testosterone levels close to the lower normal range (8 to 12 nmol/L). o Suspected or known abnormal sex hormone-binding globulin levels. Free testosterone should also be included. • Testosterone assessment is recommended in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated, including men with: o Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region; o End-stage renal disease receiving hemodialysis; o Medications that may suppress testosterone levels; o Moderate to severe chronic obstructive lung disease; o Infertility; o Osteoporosis or low-trauma fractures; o Human immunodeficiency virus infection (HIV) with sarcopenia; o Type 2 diabetes. • Luteinizing hormone serum levels should be analyzed to differentiate between primary, secondary and late-onset hypogonadism. • Testosterone replacement therapy (TRT) is recommended in patients with: o A decline in muscle mass and strength. o Reduced bone mineral density at the lumbar spine. o Decreased libido and erection. • The selection of the preparation should be a joint decision by an informed patient and the physician. • Short-acting preparations may be preferred over long-acting depot administration for initial treatment. • Human chorionic gonadotropin (hCG) treatment is only recommended for hypogonadal patients with simultaneous fertility treatment. • Perform hematological, cardiovascular, breast and prostatic assessment prior to initiating treatment. Continue hematocrit and hemoglobin monitoring, prostate-specific antigen (PSA) and digital rectal examination of prostate and breast during TRT therapy. • In patients who have undergone surgery for localized prostate cancer, testosterone therapy should not be considered for at least one year post-surgery and without PSA recurrence. • Assess response to TRT at three, six and 12 months and then annually. • In men with an abnormal bone mineral density (BMD), BMD measurements should be repeated six and 12 months after the start of TRT and thereafter annually. • Routine screening of cardiovascular effects is not indicated. • Men with cardiovascular co-morbidity should be assessed by a cardiologist before TRT is initiated and closely monitored during TRT.
The American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice**	• TRT should maintain testosterone levels within the physiologic range (280 to 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.

Clinical Guideline	Recommendations
for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002)[9]	• 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, growth of pubic and axillary hair, and phallus growth) improve with TRT. • In adolescent male patients with hypogonadotropic hypogonadism, TRT increases BMD 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.
International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, American Society of Andrology: International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, American Society of Andrology: **Recommendations: Investigation, Treatment and Monitoring of Late-Onset Hypogonadism in Males (2009)2 [11]**	• 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 BMD), TRT should be withdrawn. • 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. BMD 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 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

Clinical Guideline	Recommendations
	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 hCG 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 vs benefits of TRT is particularly important in elderly men.
American College of Physicians: **Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction (2009)**[13]	• Treatment with a 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. • 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

Clinical Guideline	Recommendations
	associated with an increased risk for non-arteritic anterior ischemic optic neuropathy.
The Endocrine Society: **Clinical Practice Guidelines: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes (2010)**[10]	• 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 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 mg to 100 mg IM weekly; or 150 mg 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 g 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 three to six 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. • 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. • BMD 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

Clinical Guideline	Recommendations
	American Urological Association/International Prostate Symptom 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.

Conclusions

The topical testosterone products included in this review are Androderm®, AndroGel®, Axiron®, Fortesta® and Testim®. The agents primarily differ in their formulations and site of administration. These products are available as gels, solutions and transdermal patches. None of these agents are currently available generically. All of the products are indicated for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).[1-6] Available head-to-head studies suggest that Testim® and AndroGel® may produce higher serum testosterone concentrations, and reduce body fat more than Androderm®.[14-17] 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®.[19] No studies are available that evaluate Axiron® or Fortesta® compared to other androgens or topical testosterone products.

According to current consensus guidelines, intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral androgen therapies are not recommended due to poor androgen effects, adverse lipid changes, and hepatic adverse events.[7-11] 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 vs another.

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