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.[1-11] 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.[1-11] 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.[12-19] 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.[17] 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.[12-19]

Table 1. Current Medications Available in the Therapeutic Class[1-11]

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:	✔

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: 75 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

Evidence-based Medicine

- Topical and miscellaneous testosterone products have been evaluated in several clinical trials.[20-33]

- 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.[21-24]
- 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®.[26]
- 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.[31]
- 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. [32]
- 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 ($P<0.001$). [33]

Key Points within the Medication Class

- According to Current Clinical Guidelines[14-17]:
    - 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.

References

1. Androderm® [package insert]. Parsippany (NJ): Actavis Pharma, Inc.; 2015 May.
2. AndroGel® 1.62% [package insert]. North Chicago (IL): AbbVie, Inc.; 2015May.
3. AndroGel® 1% [package insert]. North Chicago (IL): AbbVie, Inc.; 2015May.
4. Testim® [package insert]. Chesterbrook (PA): Auxilium Pharmaceuticals, Inc.; 2015 May.
5. Axiron® [package insert]. Indianapolis (IN): Eli Lilly & Company; 2015 May.
6. Fortesta® [package insert]. Cahadds Ford (PA): Endo Pharmaceuticals, Inc.; 2015 May.
7. Vogelxo® [package insert]. Maple Grove (MN): Upsher-Smith Laboratories, Inc.; 2014 Jun.
8. Natesto® [package insert]. Malvern (PA): Endo Pharmaceuticals, Inc.; 2015 May.
9. Striant® [package insert]. Chesterbrook (PA): Actient Pharmaceuticals LLC; 2015 May.
10. Testopel® [package insert]. Chesterbrook (PA): Auxilium Pharmaceuticals, Inc; 2015 May.
11. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2016 [cited 2016 Jun 15]. Available from: http://www.thomsonhc.com/.
12. Snyder PJ. Testosterone treatment of male hypogonadism. In: Martin KA (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 Jun 15]. Available from: http://www.utdol.com/online/index.do.
13. Snyder PJ. Clinical features and diagnosis of male hypogonadism. In: Martin KA (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 Jun 15]. Available from: http://www.utdol.com/online/index.do.
14. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, Morgentaler A. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015; 18(1): 5 to 15. Doi: 10.3109/13685538.2015.1004049.
15. Dohle GR, Arver S, Bettochi C, Jones TH, Kliesch S, Punab M. European Association of Urology: Guidelines on male hypogonadism. Male hypogonadism. 2015 Mar [cited 2015 Jun 15]. Available from: http://uroweb.org/wp-content/uploads/18-Male-Hypogonadism_LR1.pdf.
16. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS et al. The Endocrine Society. Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2010;95(6):2536-59. Available from: http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf
17. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. The Aging Male. 2009;12(1):5-12.
18. Qaseem A, Snow V, Denberg TD, Casey DE Jr., Forclea MA, Owens DK et al. Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2009;15(9):1-12.
19. Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau, LJ; American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients. Endocrine Practice. 2002 Dec;8(6):439-56. Available from: https://www.aace.com/sites/default/files/hypogonadism.pdf.
20. Kaminetsky JC, Moclair B, Hemani M, Sand M. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. J Sex Med. 2011 Apr;8(4):1186-96. doi: 10.1111/j.1743-6109.2010.02196.x. Epub 2011 Jan 26.
21. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in Hypogonadal men, with improvements in body composition and sexual function. BJU International. 2003;91:69-74.
22. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand et al. AA2500 Testosterone Gel Normalizes Androgen Levels in Aging Males with Improvements in Body Composition and Sexual Function. J Clin Endocrinol Metab. 2003;88:2673-81.
23. Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM et al. Long-term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men. J Clin Endocrinol Metab. 2000;85:4500-10.
24. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. J Clin Endocrinol Metab. 2000;85:2839-53.
25. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ et al. Long-term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men. J Clin Endocrinol Metab. 2004;89:2085-98.
26. Grober ED, Khera M, Soni SD, Espinoza MG, Lipshultz LI. Efficacy of changing testosterone gel preparations (AndroGel or Testim) among suboptimally responsive hypogonadal men. Int J Impot Res. 2008 Mar-Apr;20(2):213-7.
27. Korbonits M, Slawik M, Cullen D, Ross RJ, Stalla G, Schneider H, et al. A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. J of Clin Endo & Metab. 2004;89(5):2039-43.
28. Wang C, Ilani N, Arvert S, McLachlan RI, Soulis T, Watkinson A. Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men. Clin Endocrinol (Oxf). 2011 Dec;75(6):836-43.

29. Dobs AS, McGettigan J, Norwood P, Howell J, Waldie E, Chen Y. A novel testosterone 2% gel for the treatment of hypogonadal males. J Androl. 2012 Jul-Aug;33(4):601-7.
30. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: Results of a meta-analysis. The Journal of Urology. 2000;164:371-5.
31. Kaufman JM, Miller MG, Fitzpatrick S, McWhirter C, Brennan JJ. One-Year Efficacy and Safety Study of a 1.62% Testosterone Gel in Hypogonadal Men: Results of a 182-Day Open-Label Extension of a 6-Month Double-Blind Study. J Sex Med. 2012 Apr;9(4):1149-61.
32. Blick G, Khera M, Bhattacharya RK, Kushner H, Miner MM. Testosterone replacement therapy in men with hypogonadism and HIV/AIDS: resuts from the TRiUS registry. Postgrad Med. 2013 Mar;125(2):19-29.
33. Miner MM, Bhattacharya RK, Blick G, Kushner H, Khera M. 12-month observation of testosterone replacement effectiveness in a general population of men. Postgrad Med. 2013 Mar;125(2):8-18.