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Month/Year of Review: September 2013 **Date of Last Review:** December 2009
PDL Classes: Topical Androgens **Source Document:** Provider Synergies

Current Status of PDL Class:
- Preferred Agents: TESTOSTERONE GEL (TESTIM®), TESTOSTERONE TRANSDERMAL PATCH (ANDRODERM®), AND TESTOSTERONE CYPIONATE IM (DEPO-TESTOSTERONE®) AND TESTOSTERONE ENANTHATE IM
- Non-Preferred Agents: TESTOSTERONE TRANSDERMAL GEL (ANDROGEL® 1%/ANDROGEL® 1.62%/ANDROGEL PUMP®/ FORTESTA®), TESTOSTERONE BUCCAL (STRIANT®), TESTOSTERONE TRANSDERMAL SOLUTION (AXIRON®), PATCH, AND TESTOSTERONE PELLET IMPLANT (TESTOPEL®)

Previous Conclusions and Recommendation:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Consider including at least one gel formulation
- Consider PA criteria for coverage only for:
    - Classic hypogonadism- clinically documented with verified low testosterone levels and no contraindications. Maintenance of bone density during prolonged corticosteroid therapy
    - Maintenance of muscle mass to prevent wasting in HIV

PA Criteria: A prior authorization criterion is currently in place for androgens to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for body building and sexual dysfunction is not covered.

Conclusions and Recommendations:
- There is no new evidence that there is a difference in efficacy between the different testosterone products.
- Testosterone patches are associated with a higher incidence of adverse reactions related to administration.
- There is new low quality evidence that there is a potential increased risk of cardiovascular-related events associated with testosterone therapy, and caution should be used in older men where cardiovascular disease is common.
- There is insufficient evidence that the new formulations (Axiron®, Androgel® 1.62%, and Fortesta®) have improved efficacy or safety than other available agents.
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A Medline OVID search for randomized controlled trials (RCTs) was conducted with the following search terms: testosterone, testosterone congeners, testosterone propionate, testosterone cypionate, low testosterone, steroids, anabolic agents, androgens, hypogonadism, weight gain, and osteoporosis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to July week one 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
A systematic review and meta-analysis on the effect of androgen-replacement therapy on prostate growth was conducted by Cui, et al.[1] A literature review identified 16 RCTs with a total of 1030 patients. The quality of the RCTs was assessed using the Jadad scale, and all of the included trials were deemed to have a low risk of bias. For the 5 short term trials, 3 evaluated injected treatments compared to placebo on prostate growth (SMD 0.50, 95% CI -0.04 to 1.05; p=0.07), 2 compared transdermal application (SMD 0.30, 95% CI 0.07 to 0.54; p=0.002) and one study

evaluated oral treatment (SMD -0.02, 95% CI -0.62 to 0.60; p=0.95). For short term use, androgen replacement therapy was more likely to result in increased PSA levels than treatment with placebo when administered transdermally. Results also showed that regardless of administration method, there was no significant difference in prostate volume changes between androgen replacement therapy and placebo. Nine long term RCT's further clarified this conclusion (SMD 0.31, 95% CI -0.35 to 0.98). [1]

A systematic review and meta-analysis was conducted of placebo-controlled RCTs of testosterone therapy in men to evaluate for cardiovascular-related events.[2] A total of 27 articles were included in the systematic review and demonstrated that testosterone therapy increases composite cardiovascular-related events among men (OR 1.54, 95% CI 1.09 to 2.18, I2=7.8%). Results were similar when restricted to serious events only (OR 1.61, 95% CI 1.01 to 2.56). Previous systematic reviews have shown a non-significant increase in cardiovascular related events. The risk of cardiovascular-related events was shown to vary based on the source of funding (p=0.03) but not with baseline testosterone (p=0.70). There was not a significant increase in events in the subgroup of studies funded by the pharmaceutical industry (OR 0.89, 95% CI 0.50 to 1.60) while there was a higher risk in the subgroup of studies not funded by the pharmaceutical industry (OR 2.06, 95% CI 1.34 to 3.17). [2]

Guidelines:

The updated guidelines from the Endocrine Society for treatment of hypogonadism[3] evaluate the treatment of androgen deficiency syndromes in men. They recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes and recommend against therapy in patients with breast or prostate cancer. They give no specific recommendations based on which administration to use and recommend choice should be based on patient's preference, consideration of pharmacokinetics, treatment burden, and cost. They also recommend that clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote muscle strength. Lastly, there is a level 2 recommendation that clinicians offer testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of lean body mass and bone mineral density.

New guidelines on the treatment of male hypogonadism were released by the European Association of Urology in 2012.[4] Levels of evidence were assessed based on their level of scientific evidence and guideline recommendations were graded in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence. A Grade A recommendation is one based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial, a Grade B study is based on well-conducted clinical studies, but without randomized clinical trials, and a Grade C recommendations I made despite the absence of directly applicable clinical studies of good quality.

The guidelines recommend testosterone replacement therapy in patients with:

- A decline in muscle mass and strength (Grade A recommendation, level of evidence 1b)
- Reduced bone mideral density at the lumbar spine (Grade A recommendation, level of evidence 1a)

Decreased libido and erection (Grade B recommendation, level of evidence 3)

The following recommendations are included regarding choice of treatment:

- The patient should be fully informed about expected benefits and side effects of each treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician (Grade A recommendation, level of evidence 1a)
- Short-acting preparations may be preferred to long-acting depot administration when starting the initial treatment (Grade B recommendation, level of evidence 3).
- hCG treatment can only be recommended for hypogonadal patients with simultaneous fertility treatment (Grade B recommendation, level of evidence 1b).

No specific recommendations are given for a preferred method of delivery for testosterone therapy.

The updated guidelines for osteoporosis in men were reviewed.[5] No changes regarding the use of medications were found.

New drugs:
None

New Formulations/Indications:

FDA approved Fortesta® is a 2% strength gel available in a pump and applied to the upper thighs.[6] In an unpublished 90-day open label trial in 149 men with hypogonadism, application of Fortesta led to testosterone concentrations in the normal range in 78% of patients. [6] Skin reactions at the site of application were the most common adverse effects.

Axiron, a 2% testosterone solution, is available as a pump and is administered to the axillae, or armpit area, with an applicator.[7] This site of action theoretically minimizes the risk of transferring the drug to a family member or sexual partner. An open-label, 120 day study evaluated its use in 155 men with hypogonadism.[8] At day 120, the proportion of patients with testosterone levels within the eugonadal range was 84.1% (116/138) and significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood. Skin reactions were the most commonly reported adverse events.

An extension study up to 180 days was continued to assess skin safety and included a total of 71 patients.[9] Overall, 17% of patients had at least one new skin reaction and 3 patients discontinued due to a adverse skin reaction. The skin reaction events were often reported as a transidet stinging or burning sensation occurring immediately after application.All three products are indicated for androgen replacement therapy in adult men with primary or hypogonadotropic hypogonadism.

Testosterone gel 1.62% (Androgel) is a new strength of testosterone gel approved in 2011 for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or secondy hypogonadism.[10] Dosing and administration differ from Androgel 1% and are not interchangeable. Androgel 1.62% may not be applied to the abdomen.

Testosterone gel 1.62% was studied in a single randomized, double-blind, parallel group, placebo-controlled study through 182 days.[11] Of the 274 patients randomized, 196 completed the double-blind period. The most common adverse events leading to discontinuation was increased PSA which was prespecified as a discontinuation criterion. Results demonstrated that 82% of patients demonstrated restoration of testosterone levels and achieved an average serum testosterone level within the normal range on day 112 compared to 37% of patients on placebo ($P<0.0001$). The most common adverse events were increased PSA (9.8%), upper respiratory infection (4.7%), back pain (3.0%), headache (3%), insomnia, and hypertension (2.6%). An open label period followed to establish 1 year data.[12] On days 266 and 364, the proportion of responders for the continuing active agent group was 78.4 and 77.9%, suggesting continued efficacy for up to 1 year.

New FDA safety alerts:
None

New Trials (Appendix 1):
A total of 94 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below in addition to the trials supporting the new formulation approvals above. Please see Appendix 1 for the full abstracts.

Fennell et al conducted a small crossover study to compare the subcutaneous implant with injectable testosterone in adult males with primary or secondary hypogonadism.[13] Patients (n=38) were randomized to receive injectable or implanted testosterone for 24 to 30 weeks and then switched without a washout period to the alternative formulation. Primary endpoints were pharmacokinetic and pharmacodynamic differences between formulations.

Secondary outcomes were improvement in quality of life as measured by patient questionnaire. No statistical difference was seen in peak concentrations at week two between the two products; however, testosterone injections showed a significant drop at week four ($p< 0.001$) compared with the implant. Both formulations showed similar changes in increased hemoglobin ($p = 0.78$) and prostate specific antigens ($p = 0.44$), and decreased urea ($p = 0.15$). No differences were seen in subjects' pulse, blood pressure, or fat and lean body mass. Subjects using injectable testosterone showed a significant increase in total body weight ($p = 0.035$), while subjects using the implant had a significant increase in grip strength ($p = 0.023$). For quality of life measures, both products increased perceptions of functioning, vitality, mood, and sexual satisfaction. No statistical difference was seen between the two products for these quality of life measures. This was a poor quality trial with unclear clinical outcomes where blinding was absent, and randomization and allocation concealment were not discussed.

Aversa et al compared the efficacy of two different formulations of testosterone undecanoate in adult men with primary or secondary hypogonadism and metabolic syndrome.[14] Subjects (n = 52) were randomized to one of three parallel treatment arms: transdermal placebo gel, intramuscular (IM) or oral testosterone for six months. The primary outcomes were change from baseline in several laboratory and clinical markers including total and free testosterone, blood glucose, lipids, blood pressure and body mass index (BMI). At six months, IM testosterone subjects had significantly higher free and total testosterone compared with baseline. Oral testosterone and placebo subjects showed no significant change in concentration. No treatment showed a statistical improvement in Hbg A1c, total cholesterol, or triglycerides. IM testosterone (105 vs. 101 cm; $p < 0.0001$) showed a significant decrease in waist circumference at six months compared with baseline. No significant change was seen in blood pressure or BMI for any group. At the end of six months the oral testosterone subjects were switched to IM treatment and the trial continued for an additional six months. This was a poor quality study. Comparisons were not made between testosterone or placebo treatments but instead each arm was compared with their baseline average. Allocation concealment, randomization and blinding were not described and not all results (i.e. testosterone concentration values) were included in the published article.

References:

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6. Foresta (testosterone gel). Prescribing Information. Endo Pharmaceuticals Inc. Malvern, PA. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021015s036lbl.pdf.

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13. Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clin Endocrinol (Oxf)*. 2010;73(1):102–109. doi:10.1111/j.1365-2265.2009.03744.x.

14. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33(11):776–783. doi:10.3275/6903.

Appendix 1

Hormones - Testosterone

Goal(s):

- Cover only for covered diagnosis and for medically appropriate conditions.
- Use for body building is not covered.
- Use for sexual dysfunction is not covered.

Length of Authorization: 6 months

Preferred Alternatives: After coverage verified refer to the PDL for preferred alternatives: http://www.orpdl.org/

Requires PA: **All testosterones require PA for coverage verification**

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Does the diagnosis for the medication requested include any of the following? - Ovarian failure (256.31, 256.39) - Testicular Hypofunction (257.2) - Hypopituitarism and related disorders (253.2, 253.4, 253.7, 253.8) - AIDS-related cachexia (253.2)	**Yes**: Go to #3	**No**: Pass to RPh. RPh go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 6 months.	**No**: Go to #4
4. RPH only All other indications need to be evaluated to see if they are above the line or below the line.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

Appendix 2: Abstracts of Randomized Control Trials

Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable *vs.* implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clinical Endocrinology*. 2009. doi:10.1111/j.1365-2265.2009.03744.x.

Background Life-long testosterone replacement therapy (TRT) for younger men with organic androgen deficiency is best provided by depot testosterone (T) products. This study compared directly the two long-acting depot T products, subdermal T implants (TI) and injectable T undecanoate (TU) for maintenance of TRT.

Design, setting and participants Men with organic androgen deficiency (n = 38) undergoing regular TRT at an academic Andrology centre were recruited for a two period, randomized sequence, cross-over clinical trial without intervening wash-out period of TRT maintenance.

Outcomes For both depot T products, their pharmacokinetics and pharmacodynamics were evaluated using a range of androgen sensitive clinical, laboratory and quality of life measures as well as preference for ongoing treatment after experience of both products.

Results The two depot T products had distinct pharmacokinetics and were not bioequivalent. However, there were no consistent clinical differences in a comprehensive range of pharmacodynamics measures reflecting androgen effects on biochemistry and haematology, muscle mass and strength, and quality of life, mood and sexual function. The majority (91%) of participants chose TU over TI at study completion.

Conclusion Despite significant pharmacokinetic differences, the two depot T products are clinically interchangeable allowing for choice dependent on patient and physician delivery preference in practice but most patients preferred the injectable over the implantable form.

Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33(11):776–783. doi:10.3275/6903.

Aim: To investigate efficacy and safety of two different preparations of testosterone undecanoate (tu) in 52 hypogonadal men [mean age 57 yr and mean testosterone (t) < 320 ng/dl] with metabolic syndrome (ms).

Subjects and methods: Randomized, double-blind, double-dummy study with three parallel treatment arms [oral tu; transdermal placebo gel (p); im tu] administration for 12 months (mo). Each subject was randomized (1:1:3) to receive either oral tu (2 capsules of 40 mg/twice per day at breakfast and dinner, equalling a total dose of 160 mg/day; no.=10) for 6 mo and continued with im tu for further 6 mo, or p (3-4 g/day; no.=10) and im tu (1000 mg/12 weeks from week 6; no.=32) for 12 mo.

Results: After 6 mo, im tu increased t and free- t levels ($p<0.0001$), and improved metabolic parameters [reduction in homeostasis model assessment (homa) index, $p<0.0001$; waist circumference and fat mass, $p<0.001$, respectively], in international index of erectile function-5 and aging males' symptoms scores ($p<0.01$, respectively). After 12 months, im tu produced further increases in t and free- t levels ($p<0.0001$) and metabolic parameters (reduction in homa-index, $p<0.0001$; waist circumference $p<0.0001$; fat mass, $p<0.001$). No major adverse event due to t treatment occurred.

Conclusions: Clinical efficacy of t replacement therapy in hypogonadal men with ms is reached when its plasmatic levels approach into the medium-high range of normality (>5 ng/ml), although subjective threshold values may be different. Administration of im tu was more effective than oral tu to reach the target for t levels and to improve ms parameters. Tu was safe over 12 months and discontinuation rates were similar to placebo.