# Drugs Programs Branch Bulletin

Bulletin 2, Fall 2005

# Testosterone Products

## Ontario Drug Benefit Coverage of Testosterone Products

**Highlights of evidence and resulting Formulary coverage recommendations for testosterone products:**

- Evidence for use of testosterone products is limited to specific situations of clinically defined and symptomatic hypogonadism.
- Treatment of ageing male patients with nonspecific symptoms of hypogonadism who have no clear evidence of hypothalamic/pituitary or testicular dysfunction (i.e., men with "andropause") is ***not*** supported by the evidence, and the risks of long-term treatment are currently unknown.
- Most testosterone products, including transdermal products, will be listed as Limited Use Benefits in the Formulary.
- Criteria for Limited Use coverage of testosterone products: *For male patients with confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary, or testicular disease, or in HIV-infected patients. Note: older males with nonspecific symptoms of fatigue, malaise, or depression who have a low-normal random testosterone level do not satisfy these criteria.*
- The changes will be implemented on March 1, 2006, to allow time for physicians, pharmacists, and patients to manage the transition without adversely affecting patient care. The new products, Androderm 12.2 mg and Androgel, were listed as Limited Use Benefits effective February 22, 2005, with Update F to Ed. 38 of the Formulary.

## Purpose of this Communication

To outline key recommendations by the Drug Quality and Therapeutics Committee (DQTC) to physicians and pharmacists about coverage of testosterone products on the Ontario Drug Benefits (ODB) Program formulary, and to outline the process by which those recommendations were made.

## DQTC and Health Care Professionals: Shared Values and Processes

**Health care providers and the DQTC share the goal of optimal health outcomes.**

The goals of the DQTC and health care professionals are similar: optimal health outcomes for patients. The DQTC focuses on the evidence from clinical trials and compares the merits of a drug to others in the same class. The DQTC's mandate also includes maximizing value for cost, so it takes a societal perspective in making recommendations.

For more information about the DQTC and the Formulary review process, please refer to the Drug Programs Branch Bulletin – Hormone Replacement Products, Bulletin 1, 2005.

## Testosterone Product Review Results

The DQTC review of products for testosterone replacement was conducted in 2003-04 to ensure that ODB Formulary coverage reflects current clinical knowledge and data for efficacy, safety, and cost-effectiveness. For this review, input from urology, endocrinology, geriatric specialists, and family physicians was considered. The DQTC's updated coverage recommendations for these products are described beginning on page 3.

## Overview of the Evidence for Testosterone Replacement

Testosterone replacement therapy is indicated for men with clinically defined and symptomatic primary or secondary hypogonadism. Cryptorchidism, Klinefelter's syndrome, and orchidectomy can cause primary hypogonadism. Secondary hypogonadism can be caused by pituitary-hypothalamic injury due to tumours, trauma, or radiation.

**Conditions associated with mild hypogonadism should be treated with proven therapies, e.g., antidepressants for depression, bisphosphonates for osteoporosis.**

In recent years, testosterone therapy has been advocated for the treatment of symptoms attributed to "male menopause" or "andropause" (ageing male patients with nonspecific symptoms of hypogonadism who have no clear evidence of hypothalamic/pituitary or testicular dysfunction), as well as improvement of sexual function in women. The "pros" and "cons" evaluating the use of testosterone products in such ageing male patients are presented in the table below.

**The long-term risks of testosterone therapy have not been well evaluated. Studies of the long-term effects of testosterone in men and women are needed.**

## Pros and Cons of Treatment of Ageing Male Patients with Nonspecific Symptoms

| PROS |
|---|
| Symptoms may respond to testosterone treatment (1) |
| Bone mineral density may be improved (1) |
| **CONS** |
| Defining hypogonadism in these patients is problematic:<br>• Serum testosterone levels decline normally with age (1), so interpretation of low levels is difficult<br>• Testosterone levels are affected by diurnal variation, stress, drug interactions, and other factors<br>• Low levels are defined compared to younger controls (20-40 year olds)<br>• Accurate measurement is difficult because testosterone is highly bound to sex hormone binding globulin (SHBG): levels of total and free testosterone decrease with age, but SHBG levels increase (1,3)<br>– Access to bioavailable testosterone measurement is not uniform in Ontario |
| Symptoms may reflect conditions that should be treated with proven therapies, e.g., antidepressants for depression, bisphosphonates for osteoporosis<br>• No direct comparative trials vs. standard therapy for osteoporosis (bisphosphonates) have been conducted<br>• The effect of testosterone therapy on fracture rates has not been determined |
| Risks of long-term testosterone treatment have not been adequately evaluated |
| Testosterone treatment risks may include:<br>• Increased cardiovascular risks, due to increased LDL and decreased HDL (with oral androgens) (1)<br>• Increased hematocrit and hemoglobin levels (2)<br>• Increased PSA levels (though whether there is increased prostate cancer risk is currently unknown) (2,3)<br>• Burn-like reactions and blistering at transdermal patch application site (3,4) |

## DQTC Recommendations about Testosterone Products

**Most testosterone products, including transdermal patches, will be listed as Limited Use Benefits in the Formulary.**

Given the overwhelming lack of evidence to support treatment of ageing male patients with nonspecific symptoms of hypogonadism and no clear evidence of hypothalamic/pituitary or testicular dysfunction, the DQTC recommended that the following testosterone products be listed as Limited Use (LU) benefits in the ODB Formulary: Andriol, Depo-Testosterone, Delatestryl, Androderm (12.2 mg strength only), and Androgel. The DQTC's recommendation for LU listing reflects their evaluation regarding the cost-effective use of these drugs as well as the need for appropriate monitoring and regular assessment. The LU criteria are provided in the box below. These listings represent the following changes: transdermal products are now listed, and oral and depot products have been changed to a Limited Use listing. Access has been increased to transdermal products as a cost-effective alternative to allow greater physician and patient choice. It is of note that the DQTC considered health system costs (e.g., physician office visits for injectable products), in addition to drug costs in assessing the cost-effectiveness of these products.

**Criteria for Limited Use coverage of testosterone products:**

**Reason for Use (RFU) Code: 397**

*For male patients with confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary, or testicular disease, or in HIV-infected patients.*

*Note: older males with nonspecific symptoms of fatigue, malaise, or depression who have a low-normal random testosterone level do not satisfy these criteria.*

Patients who do not meet the Limited Use criteria may be considered for coverage through the Section 8 (Individual Clinical Review) mechanism. Please note that insufficient evidence is available to support use of these products in:

- older males with low-normal random testosterone levels and nonspecific symptoms of fatigue, malaise, depression
- male patients with PSA levels greater than their age-specific normal levels.

For more information on the Section 8 process, see Part VIII of the Formulary (http://www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html).

In the absence of sufficient evidence, testosterone use in women was not approved for listing in the Formulary, and will be reassessed when more data are available.

Testosterone is contraindicated in patients with prostate cancer and benign prostatic hypertrophy. Therefore, an examination for prostate cancer prior to initiation of treatment, as well as a baseline PSA level, has been recommended by manufacturers (4).

## Cost Comparison of Testosterone Products

| Drug | Strength | Average Dose for Male Hypogonadism | Formulary Status (As of March 1, 2006) | Average Monthly Drug Cost ($) |
|---|---|---|---|---|
| Androderm (testosterone patch) | 12.2mg | 2 patches qhs | Limited Use* | 113 |
| Androderm (testosterone patch) | 24.3mg | 1 patch qhs | Not listed | 113 |
| Androgel (testosterone gel) | 2.5g<br>5g | 5g od | Limited Use* | 113 |
| Andriol (testosterone undecanoate) | 40mg capsule | 120-160mg od | Limited Use | 85 – 113 |
| Depo-testosterone (testosterone cypionate) | 100mg/mL injection | 200-400mg IM q 3-4 weeks | Limited Use | 43 – 72† |
| Delatestryl (testosterone enanthate) | 1000mg/5mL injection | 100-400mg IM q 4 weeks | Limited Use | 42 – 54† |

* Androderm 12.2mg and Androgel were listed as LU benefits effective February 22, 2005, with Update F to Ed. 38 of the Formulary.

† Based on drug cost per vial plus estimated costs for physican office visits.

## Implementation

The Formulary listing changes noted on page 3 will be implemented on March 1, 2006. This will allow time for physicians, pharmacists and patients to manage the transition without negatively affecting patient care. Physicians may wish to complete a Limited Use (LU) prescription for patients who meet the LU criteria for oral and injectable testosterone products during this transition period. This will ensure that the LU prescription is on file at the dispensing pharmacy when the listing changes take effect. Pharmacists should continue submitting claims for these products as General Benefits until the effective date of the listing change. The new products, Androderm 12.2mg and Androgel, were listed as LU benefits effective February 22, 2005, with Update F to Ed. 38 of the Formulary.

## Additional information on Testosterone Therapy

For additional information about testosterone replacement therapy, visit the web sites listed below.

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients – 2002 Update. Found at www.aace.com/clin/guidelines/hypogonadism.pdf, accessed September 10, 2004.

Health links: men's health. Ontario Ministry of Health and Long-Term Care. Found at http://www.health.gov.on.ca/english/hlinks/men.html, accessed September 9, 2004.

Male Hypogonadism. Merck Manual, Sec. 19, Ch. 269, Endocrine and Metabolic Disorders. Found at http://www.merck.com/mrkshared/mmanual/section19/chapter269/269g.jsp, accessed September 13, 2004.

Testosterone therapy: The answer for aging men? Mayo Clinic. Found at http://www.mayoclinic.com/invoke.cfm?objectid=671310EE-FD49-43AB-80A5A9AEB5AD7EDD, accessed January 12, 2005.

## References


1. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients – 2002 Update. Endocrine Practice 2002;8. Found at www.aace.com/clin/guidelines/hypogonadism.pdf, accessed September 10, 2004.
2. Anawalt BD, Merriam GR. Neuroendocrine aging in men. Endocrinol Metab Clin North Am 2001;30:647-666.
3. Lund BC, Bever-Stille KA, Perry PJ. Testosterone and andropause: the feasibility of testosterone replacement therapy in elderly men. Pharmacotherapy 1999;19:951-956.
4. Compendium of Pharmaceuticals and Specialties. 2003. Ottawa: Canadian Pharmacists Association.


**Your feedback on this bulletin is welcome.**


Drug Programs Branch
5700 Yonge Street, 3rd Floor, Toronto, Ontario  M2M 4K5
Tel: 416-327-8109 or 1-866-811-9893
Fax: 416-327-8123 (general); 416-327-7526 or 1-866-811-9908 (ICR requests)
TTY: 1-800-387-5559
E-mail: DrugPrograms@moh.gov.on.ca
Web: www.health.gov.on.ca


Or call the Ministry INFOline at 1-800-268-1154 (Toll-free in Ontario only); TTY: 1-800-387-5559

This bulletin and previous Drug Programs Branch bulletins are available on-line at http://www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html

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