

Flaxseed Supplement Curbed Vasomotor Symptoms

BY BRUCE JANCIN

Denver Bureau

SAN ANTONIO — Flaxseed relieved vasomotor hot flashes in postmenopausal women in a randomized blinded crossover trial. Lorraine E. Turner, Ph.D., reported at the annual breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Although the study wasn't conducted in women with a history of breast cancer, the

observed benefits suggest that flaxseed could be a useful treatment alternative in such patients, who frequently experience hot flashes exacerbated by adjuvant chemotherapy and/or hormone therapy with tamoxifen, observed Dr. Turner of the University of Manchester, England.

The predicament breast cancer patients face with regard to hot flashes is that hormone therapy is the most effective treatment for these estrogen deficiency-related symptoms, but there is concern that

such therapy might increase the risk of breast cancer recurrence.

Dr. Turner reported on 85 postmenopausal women who experienced at least five hot flashes and/or night-sweat episodes per 24 hours. They were randomized to 40 g/day of flaxseed food supplements or placebo for 3 months and then crossed over to the opposite treatment arm for another 3 months of therapy.

The median number of hot flashes dropped by 38% during flaxseed supplementa-

tion from a baseline of 208 per month, with placebo showing no significant effect. The decline in hot flashes correlated with a rise in enterodiol, enterolactone, and other urinary lignan markers. Lignans are a type of phytoestrogen abundant in flaxseed.

Laboratory work performed on a monthly basis showed that flaxseed supplementation was associated with significant reductions in serum FSH and Apo-A1, but no changes were seen in serum total cholesterol, triglycerides, growth hormone, LH, prolactin levels, or markers of bone turnover.

Nor was flaxseed associated with any thyroid function abnormalities. This is an important observation, because although soy isoflavones previously have been shown to reduce hot flashes while improving serum lipid profiles and enhancing bone mineral density, there is some evidence to suggest isoflavones can cause hypothyroidism, she said.

Dr. Turner's study was funded by the Food Standards Agency of the United Kingdom.

Anastrozole Is A Cost-Effective Alternative

SAN ANTONIO — Anastrozole is a cost-effective alternative to generic tamoxifen for primary adjuvant therapy in postmenopausal women with early-stage breast cancer, according to a new economic analysis.

Based upon the 68-month efficacy and safety data from the Arimidex, Tamoxifen, Alone or Together (ATAC) trial, 5 years of adjuvant anastrozole cost an estimated \$23,740 per quality-adjusted life-year gained beyond that achieved with 5 years of tamoxifen, Gershon Y. Locker, M.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center. (See related story, next page.)

That's well within the bounds of what's considered reasonably cost-effective and reimbursable by U.S. health care standards, which variously define the threshold for cost-effectiveness as \$50,000-100,000 per quality-adjusted life-year, noted Dr. Locker of Evanston (Ill.) Northwestern Healthcare and Northwestern University.

The estimated incremental cost-effectiveness for anastrozole compared to tamoxifen was \$29,132 per life-year gained without considering quality of life, he added. His analysis used published (2004 Drug Topics Red Book) wholesale acquisition costs of \$6.56/day for anastrozole (Arimidex) and \$1.33/day for tamoxifen.

The study factored in the direct medical costs of the increased rates of recurrent breast cancer, stroke, venous thromboembolism, and other adverse events associated with tamoxifen therapy, as well as the greater fracture risk entailed in anastrozole therapy.

—Bruce Jancin



Rx only

Brief Summary (for full Prescribing Information and Patient Information, refer to package insert).

INDICATIONS AND USAGE

AndroGel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

1. Primary hypogonadism (congenital or acquired) — testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

2. Hypogonadotropic hypogonadism (congenital or acquired) — idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men usually have testosterone serum levels but have gonadotropins in the normal or low range.

AndroGel has not been clinically evaluated in males under 18 years of age.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

AndroGel is not indicated for use in women, has not been evaluated in women, and must not be used in women.

Pregnant women should avoid skin contact with AndroGel application sites in men. Testosterone may cause fetal harm. In the event that unwashed or undried skin to which AndroGel has been applied does come in direct contact with the skin of a pregnant woman, the general area of contact on the woman should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

AndroGel should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy.

WARNINGS

1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone is not known to produce these adverse effects.

2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

3. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for surveillance men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).

4. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

6. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

7. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.

PRECAUTIONS

Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site. The following precautions are recommended to minimize potential transfer of testosterone from AndroGel-treated skin to another person:

- Patients should wash their hands immediately with soap and water after application of AndroGel.
- Patients should cover the application site(s) with clothing after the gel has dried (e.g., a shirt).
- In the event that unwashed or undried skin to which AndroGel has been applied does come in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.

General

The physician should instruct patients to report any of the following:

- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color, or ankle swelling.
- Breathing disturbances, including those associated with sleep.

Information for Patients

Advise patients to carefully read the information brochure that accompanies each carton of AndroGel single-use packets or AndroGel Pump.

Advise patients of the following:

- AndroGel should not be applied to the scrotum.
- AndroGel should be applied once daily to clean dry skin.
- After application of AndroGel, it is currently unknown for how long showering or swimming should be avoided. For optimal absorption of testosterone, it appears reasonable to wait at least 5-6 hours after application prior to showering or swimming. Nevertheless, showering or swimming after just 1 hour should have a minimal

effect on the amount of AndroGel absorbed if done very infrequently.

- Since alcohol based gels are flammable, avoid fire, flame or smoking until the gel has dried.

Laboratory Tests

1. Hemoglobin and hematocrit levels should be checked periodically to detect polycythemia in patients on long-term androgen therapy.

2. Liver function, prostatic specific antigen, cholesterol, and high-density lipoprotein should be checked periodically.

3. To ensure proper dosing, serum testosterone concentrations should be measured (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Propranolol: In a published pharmacokinetic study of an injectable testosterone product, administration of testosterone propionate led to an increased clearance of propranolol in the majority of men tested.

Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus, these drugs should be administered cautiously, particularly in patients with cardiac or hepatic disease.

Drug/Laboratory Test Interactions Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroxine hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility **Animal Data:** Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human Data: There are rare reports of hepatocellular carcinomas in patients receiving long-term oral therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for surveillance men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).

Pregnancy Category X (see CONTRAINDICATIONS) — Teratogenic Effects: AndroGel is not indicated for women and must not be used in women.

Nursing Mothers: AndroGel is not indicated for women and must not be used in women.

Pediatric Use: Safety and efficacy of AndroGel in pediatric patients have not been established.

ADVERSE REACTIONS In a controlled clinical study, 154 patients were treated with AndroGel for up to 6 months (see Clinical Studies). Adverse Events possibly, probably or definitely related to the use of AndroGel and reported by ≥1% of the patients are listed in Table 1.

Table 1. Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel in the Controlled Clinical Trial

Adverse Event	Dose of AndroGel®		
	5 g	7.5 g	10 g

Acne	1%	3%	6%
Alpecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder	3%	0%	0%

* Lab test abnormal occurred in nine patients with one or more of the following events: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, or elevated total bilirubin.

** Prostate disorders included five patients with enlarged prostate, one patient with BPH, and one patient with elevated PSA results.

The following adverse events possibly related to the use of AndroGel occurred in fewer than 1% of patients: amnesia, anxiety, discoloration of hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

In the clinical trial of AndroGel, skin reactions at the site of application were occasionally reported with AndroGel, but none was severe enough to require treatment or discontinuation of drug.

Six (4%) patients in this trial had adverse events that led to discontinuation of AndroGel. These events included the following: cerebral hemorrhage, convulsion (neither of which was considered related to AndroGel administration), depression, sadness, memory loss, elevated prostatic specific antigen and hypertension. No AndroGel patients discontinued due to skin reactions.

In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with AndroGel: these were asthenia and depression in one patient and increased libido and hyperkinesia in the

other. Among 17 patients in foreign clinical studies there was 1 instance each of acne, erythema and benign prostatic adenoma associated with a 2.5% testosterone gel formulation applied dorsally.

One hundred six (100) patients have received AndroGel for up to 12 months in a long-term follow-up study for patients who completed the controlled clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table 2 summarizes those adverse events possibly, probably or definitely related to the use of AndroGel and reported by at least 1% of the total number of patients during long-term exposure to AndroGel.

Table 2. Incidence of Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel in the Long-Term, Follow-up Study I

Adverse Event	Dose of AndroGel®		
	5 g	7.5 g	10 g

Lab Test Abnormal*	4.2%	0.0%	6.3%
Peripheral Edema	1.4%	0.0%	3.1%
Acne	2.8%	0.0%	12.5%
Application Site Reaction	9.7%	10.0%	3.1%
Prostate Disorder**	2.8%	5.0%	18.8%
Urination Impaired	2.8%	0.0%	0.0%

* Lab test abnormal included one patient each with elevated GGT, elevated hematocrit and hemoglobin, increased total bilirubin, worsened hyperlipidemia, decreased HDL, and hypokalemia.

** Prostate disorders included enlarged prostate, elevated PSA results, and in one patient, a new diagnosis of prostate cancer; three patients (one taking 7.5 g daily and two taking 10 g daily) discontinued AndroGel treatment during the long-term study because of such disorders.

DRUG ABUSE AND DEPENDENCE

AndroGel contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act of 1990.

Oral ingestion of AndroGel will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

OVERDOSAGE

There is one report of acute overdose by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

The recommended starting dose of AndroGel 1% is 5 g delivering 5 mg of testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily AndroGel 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g as instructed by the physician.

AndroGel is available in either unit-dose packets or multiple-dose pumps. The metered-dose pump delivers 1.25 g of product when the pump mechanism is fully depressed once.

AndroGel must not be applied to the genitals.

If using the multi-dose AndroGel Pump, patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g of product required to achieve the daily prescribed dosage. The product may be delivered directly into the palm of the hand and then applied to the desired application site, either one pump actuation at a time or upon completion of all pump actuations required for the daily dose. Please refer to the chart below for specific dosing guidelines when the AndroGel pump is used.

Prescribed Daily Dose	Number of Pump Actuations
5 g	4 (once daily)
7.5 g	6 (once daily)
10 g	8 (once daily)

If using the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after AndroGel has been applied.

HOW SUPPLIED

AndroGel 1% is supplied in non-aerosol, metered-dose pumps. The pump is composed of plastic and stainless steel and an LDPE/aluminum foil liner, liner encased in rigid plastic with a polypropylene cap. Each individual packaged 88 g AndroGel Pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

AndroGel 1% is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

NDC Number **Package Size**
0051-8485-33 75 g pump (dispenses 60 metered 1.25 g doses)
0051-8488-88 2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses)

0051-8425-30 30 packets (2.5 g per packet)
0051-8450-30 30 packets (5 g per packet)

Keep AndroGel out of the reach of children.
Manufactured by:
Laboratories Besins International
Montroque, France

For:
United Pharmaceuticals, Inc.
A Solvay Pharmaceuticals, Inc. Company
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