

# Intensive Glycemic Control Protects Kidneys

BY DIANA MAHONEY

FROM KIDNEY WEEK 2011

PHILADELPHIA – Early, intensive treatment for type 1 diabetes with conventional therapy halves the long-term risk of developing an impaired glomerular filtration rate, the common pathway leading to end-stage kidney disease, Dr. Ian H. de Boer said at the meeting.

He reported new data from the Dia-

betes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrating a nearly 50% reduction in the risk of glomerular filtration rate (GFR) impairment – defined as an incident estimated GFR less than 60 mL/min per 1.73 m<sup>2</sup> of body surface area at two consecutive study visits – among individuals randomly assigned to intensive diabetes

treatment versus those assigned to conventional treatment over a 22-year median follow-up.

In the multicenter DCCT, 1,441 individuals with type 1 diabetes were randomized to 6.5 years of conventional therapy (730 patients), consisting of one or two insulin injections daily designed to prevent hyperglycemic symptoms, or to intensive diabetes treatment (711 patients), consisting of three or more in-

sulin injections daily or the use of an insulin pump in an attempt to achieve a glycated hemoglobin level of less than 6.05%, “as close to the nondiabetic range as possible,” Dr. de Boer reported at the meeting sponsored by the American Society of Nephrology.

The study population included patients in a primary intervention cohort who had diabetes for 1-5 years with an albumin excretion rate of less than 40 mg per 24 hours and no retinopathy and those in a secondary intervention cohort with a 1- to 15-year history of diabetes, an albumin excretion rate of 200 mg or less per 24 hours, and no more than moderate nonproliferative retinopathy, he noted.

Of the DCCT participants, 1,375 agreed to participate in the observational extension EDIC study, including a statistically similar number of patients from the intensive and conventional therapy groups, Dr. de Boer reported. As per the protocol of both studies, serum creatinine levels were measured annually.

The mean hemoglobin A<sub>1c</sub> level during the DCCT was 7.3% in the intensive treatment group and 9.1% in the conventional therapy group. “In the EDIC years 1-16, the mean hemoglobin A<sub>1c</sub> was nearly 8% in each group, with no clinically or statistically significant difference,” said Dr. de Boer of the University of Washington in Seattle.

During the combined 22 years of follow-up for both studies, “70 patients developed impaired [GFR], including 24 who had been assigned to intensive therapy and 46 who received conventional treatment,” Dr. de Boer stated, noting that most of the cases occurred during the EDIC study period.

The time of the events is important, he said. “Only 4 of the 70 occurred during DCCT, and 66 occurred during EDIC study follow-up. Almost all of the events occurred more than 10 years after randomization.”

The intensive therapy reduced the risk of impaired GFR by 50%, according to statistical analyses, Dr. de Boer said. Twenty years after randomization, “the cumulative incidence of an impaired GFR was 2.0% among those assigned to intensive therapy and 5.5% in those assigned to conventional therapy,” representing an absolute risk reduction of 3.5%, he explained.

The study results were reported concurrently with the online publication of the data (N. Engl. J. Med. 2011;365:2366-76).

The study was funded by U.S. government grants and through a Genentech Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. Abbott, Animas, Aventis, Bayer, Becton Dickinson, Can Am, Eli Lilly, LifeScan, Medtronic, MiniMed, Omron, OmniPod, Roche, and Sanofi-Aventis provided research supplies or equipment and the University of Washington received support from Abbott Laboratories.

## ANDRODERM<sup>®</sup>

(testosterone transdermal system)

### BRIEF SUMMARY

For full Prescribing Information, see package insert.

### INDICATIONS AND USAGE

ANDRODERM is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
- **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 have low testosterone serum concentrations but have gonadotropins in the normal or low range.

**Important limitations of use** – Safety and efficacy of ANDRODERM in males <18 years old have not been established [see Use in Specific Populations].

### CONTRAINDICATIONS

- ANDRODERM is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate [see Warnings and Precautions].
- ANDRODERM is contraindicated in women who are, or who may become pregnant, or who are breastfeeding. ANDRODERM may cause fetal harm when administered to a pregnant woman. ANDRODERM may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to ANDRODERM, she should be apprised of the potential hazard to the fetus [see Use in Specific Populations].

### WARNINGS AND PRECAUTIONS

#### Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It is appropriate to re-evaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices [see Contraindications].

#### Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It is appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then monitor annually. Discontinue testosterone therapy if the hematocrit becomes elevated. Testosterone therapy may be restarted when the hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

#### Use in Women and Children

**Women and children should not use ANDRODERM. Use in women and children has not been studied with ANDRODERM.**

Due to lack of controlled studies in women and potential virilizing effects, ANDRODERM is not indicated for use in women and children [see Contraindications and Use in Specific Populations].

#### Potential for Adverse Effects on Spermatogenesis

At large doses of exogenous androgens, including ANDRODERM, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) that could lead to adverse effects on semen parameters including reduction of sperm count.

#### Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. ANDRODERM is not known to cause these adverse effects.

#### Edema

Androgens, including ANDRODERM, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease [see Adverse Reactions].

#### Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including ANDRODERM, for hypogonadism.

#### Sleep Apnea

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

#### Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

#### Hypercalcemia

Androgens, including ANDRODERM, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

#### Decreased Thyroxine-Binding Globulin

Androgens, including ANDRODERM, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentration and increased resin uptake of T3 and T4. Free thyroid hormone concentration remains unchanged and there is no clinical evidence of thyroid dysfunction.

### ADVERSE REACTIONS

#### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 1 shows the adverse reactions that were reported by > 3% of 36 hypogonadal men who were treated with ANDRODERM 2 mg/day, 4 mg/day, or 6 mg/day for 28 days. Of note, all hypogonadal men studied had been stable users of topical testosterone replacement products prior to the study and there was no washout period between therapies. Furthermore, there was only one subject titrated to 6 mg/day and he withdrew from the study prematurely.

**Table 1. Adverse Reactions Seen With the Use of ANDRODERM 2 mg/day, 4 mg/day, or 6 mg/day (> 3%)**

Adverse Reaction	Overall N = 36 %
Application site pruritus	17
Application site vesicles	6
Back pain	6

Other less common adverse reactions reported by < 3% of patients included: application site erythema, application site exfoliation, chills, diarrhea, fatigue, gastroesophageal reflux disease, hemarthrosis, hematuria, headache, polyuria, and prostatitis. The overall incidence of application site reactions of any kind was 28% (10 subjects with 13 adverse reactions).

No serious adverse reactions to ANDRODERM 2 mg/day and 4 mg/day were reported during the clinical trial.

Table 2 shows the adverse reactions that were reported in > 3% of 122 patients in clinical studies with ANDRODERM dosage strengths of 2.5 mg/day, 5 mg/day, and 7.5 mg/day. The most common adverse reactions reported were application site reactions. Transient mild to moderate erythema was observed at the site of application in the majority of patients at some time during treatment. The overall incidence of application site reactions of any kind was 48% (59 subjects with 107 adverse reactions).

**Table 2. Adverse Reactions Seen With the Use of ANDRODERM 2.5 mg/day, 5 mg/day, or 7.5 mg/day (> 3%)**

Adverse Reaction	Overall N = 122 %
Application site pruritus	37
Application site blistering	12
Application site erythema	7
Application site vesicles	6
Prostate abnormalities	5
Headache	4
Contact dermatitis to system	4
Application site burning	3
Application site induration	3
Depression	3

The following reactions occurred in less than 3% of patients: rash, gastrointestinal bleeding, fatigue, body pain, pelvic pain, hypertension, peripheral vascular disease, increased appetite, accelerated growth, anxiety, confusion, decreased libido, paresthesia, thinking abnormalities, vertigo, acne, bullae at application site, mechanical irritation at application site, rash at application site, contamination of application site, prostate carcinoma, dysuria, hematuria, impotence, urinary incontinence, urinary tract infection, and testicular abnormalities.

### DRUG INTERACTIONS

#### Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.

#### Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

#### Corticosteroids

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored, particularly in patients with cardiac, renal or hepatic disease.

#### Triamcinolone

• The topical administration of 0.1% triamcinolone cream to the skin under the central drug reservoir prior to the application of the ANDRODERM system did not significantly alter transdermal absorption of testosterone; however, the rate of complete adherence was lower.

• Pretreatment with triamcinolone ointment formulation significantly reduced testosterone absorption from the ANDRODERM system.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Pregnancy Category X [see Contraindications] — ANDRODERM is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

#### Nursing Mothers

Although it is not known how much testosterone transfers into human milk, ANDRODERM is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation [see Contraindications].

#### Pediatric Use

Safety and efficacy of ANDRODERM have not been established in males < 18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

#### Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing ANDRODERM to determine whether efficacy in those over 65 years of age differs from younger patients. Additionally, there are insufficient long-term safety data in geriatric patients utilizing ANDRODERM to assess a potential incremental risk of cardiovascular disease and prostate cancer.

#### Renal Impairment

No studies were conducted in patients with renal impairment.

#### Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

### DRUG ABUSE AND DEPENDENCE

#### Controlled Substance

ANDRODERM contains testosterone, a Schedule III controlled substance under the Anabolic Steroids Control Act.

#### Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

#### Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drug are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of withdrawal syndrome upon discontinuation of anabolic steroid use

### OVERDOSAGE

No cases of overdose with ANDRODERM have been reported in clinical trials. There is one report of acute overdose by injection of testosterone enanthate: testosterone concentrations of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdose would consist of discontinuation of ANDRODERM together with appropriate symptomatic and supportive care.

For all medical inquiries contact:  
Watson Medical Communications  
Parsippany, NJ 07054  
800-272-5525

**Watson**<sup>®</sup>

Manufactured By:  
Watson Laboratories, Inc.  
Salt Lake City, UT 84108 USA  
Distributed By:  
Watson Pharma, Inc.  
Parsippany, NJ 07054 USA

**Rx Only** Revised: October 2011