

# **PRODUCT MONOGRAPH**

## **ANDRIOL**

(Testosterone undecanoate)

**40 mg capsules**

## **ANDROGEN**

**Organon Canada Ltd./Ltée.**  
200 Consilium Place  
Suite 700  
Scarborough, Ontario  
**M1H 3E4**

Date of Preparation:  
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**5HN855633**

## NAME OF THE DRUG

ANDRIOL

(testosterone undecanoate)

40 mg capsules

## PHARMACOLOGICAL CLASSIFICATION

Androgen

## ACTIONS AND CLINICAL PHARMACOLOGY

Andriol (testosterone undecanoate), an orally active testosterone preparation, is a fatty acid ester of the natural androgen testosterone. Unlike other oral testosterone preparations, testosterone undecanoate is able to by-pass the liver via the lymphatic system and is therefore orally bioavailable.

Therapy with Andriol increases plasma levels of testosterone and its active metabolites, leading to a regular therapeutic effect. In eugonadal men, peak testosterone levels are reached in approximately 4-5 hours after ingestion returning to basal levels after about 10 hours. In volunteers and hypogonadal men, 77-93% of an orally administered dose of testosterone undecanoate was excreted in the urine and **faeces** within 3 to 4 days.

### INDICATIONS AND CLINICAL USE

Andriol (testosterone undecanoate) is indicated for replacement therapy in males in conditions associated with symptoms of deficiency or absence of endogenous testosterone: for the management of congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism; to develop and maintain secondary sexual characteristics in males with testosterone deficiency. Andriol is also indicated to stimulate puberty in carefully selected males with clearly delayed puberty not secondary to pathological disorder.

It is also used as replacement therapy in impotence or for male climacteric symptoms when the conditions are due to a measured or documented androgen deficiency.

### CONTRAINDICATIONS

Known hypersensitivity to any of the components of the product; males with carcinoma of the breast; males with known or suspected carcinoma of the prostate gland; patients with serious cardiac, hepatic or renal disease; hypercalcemia; impaired liver function; prepubertal males; patients easily stimulated sexually. Androgens are also contraindicated in patients with nephrosis or the **nephrotic** phase of nephritis.

### WARNINGS

Hypercalcemia may occur in immobilized patients and in patients with breast cancer. If this occurs, the drug should be discontinued.

Prolonged use of high doses of androgens (principally the **17-alpha-alkyl-androgens**) has been associated with development of hepatic adenomas, hepatocellular carcinoma and peliosis hepatis •

all potentially life-threatening complications.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkyl-androgens. Should this occur, the drug should be discontinued. This is reversible with discontinuation of the drug.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

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

Gynecomastia may develop and occasionally persists in patients being treated for hypogonadism. Androgen therapy should be used cautiously in males with delayed puberty. Androgens can accelerate bone maturation without producing compensatory gain in linear growth. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every six months. These adverse effects may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

### PRECAUTIONS

Patients with benign prostatic hypertrophy may develop acute urethral obstruction. Priapism or excessive sexual stimulation may develop. Oligospermia may occur after prolonged administration or excessive dosage. If any of these effects appear, the androgen should be stopped and if restarted, a lower dosage should be utilized.

## Drug Interactions

Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens are started and stopped. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

May potentiate cyclosporine and increase risk of nephrotoxicity.

Concurrent use of somatrem or somatropin with androgens in prepubertal males may accelerate epiphyseal maturation.

Increased serum oxyphenbutazone concentrations have been reported with concurrent administration of androgen and oxyphenbutazone.

May interact with adrenocorticoids: glucocorticoids, especially with significant mineralocorticoid activity; mineralocorticoids; or corticotropins, especially prolonged use; sodium-containing medications or foods.

Laboratory Test Interference:

Alterations may occur in the following clinical laboratory tests:

metirapone test, fasting blood sugar (**FBS**) and glucose tolerance test, thyroid function tests (decrease in thyroxine-binding capacity and radioactive iodine uptake, and an increase in T3 uptake by the red blood cells or resin; free thyroxine levels remain unchanged);

electrolytes (retention of sodium chloride, water, potassium, calcium, and inorganic phosphates),

blood coagulation tests (suppression of clotting factors II, V, VII, and **X**), alteration to liver

function tests, increased serum cholesterol and miscellaneous laboratory tests (decreased

creatinine and **creatinine** excretion lasting up to 2 weeks after discontinuing therapy). Androgens enhance blood fibrinolytic activity and increase hematocrit and serum hemoglobin levels; effects on plasma lipids are variable. Administration of testosterone, but not the **17-alpha-alkyl** substituted derivatives, elevates the level of urinary 17-ketosteroids.

### Laboratory Tests

Because of the hepatotoxicity associated with the use of **17-alpha-alkylated** androgens, liver function tests should be obtained periodically.

Hemoglobin and hematocrit levels (to detect polycythemia) should be checked periodically in patients receiving long-term androgen administration.

Serum cholesterol may increase during androgen therapy.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effect of androgen therapy on the epiphyseal centers.

### ADVERSE REACTIONS

The following adverse reactions have occurred with androgen therapy: inhibition of testicular function, testicular atrophy and oligospermia, impotence, gynecomastia, epididymitis and bladder irritability, excessive frequency and duration of penile erections, nausea, **cholestatic** jaundice, peliosis hepatis, polyerythemia, headache, anxiety, depression, generalized paresthesia and rarely anaphylactoid reaction. In addition, the following reactions are known to occur with anabolic steroids: increased or decreased libido, flushing of the skin, acne, habituation, excitation and sleeplessness, chills, leukopenia, and bleeding in patients on concomitant anticoagulant therapy.

There have been rare reports of hepatocellular carcinoma, particularly in association with **long-term** therapy, in patients receiving methyltestosterone or other androgenic and anabolic steroids.

### SYMPTOMS AND TREATMENT OF OVERDOSAGE

No experience with overdosage has been reported. No specific antidote is available.

### DOSAGE AND ADMINISTRATION

The dosage should be adjusted according to the response of the individual patient.

Usually, an initial dosage of 120-160 mg daily in two divided doses for 2-3 weeks is adequate, followed by a maintenance dosage of 40-120 mg daily.

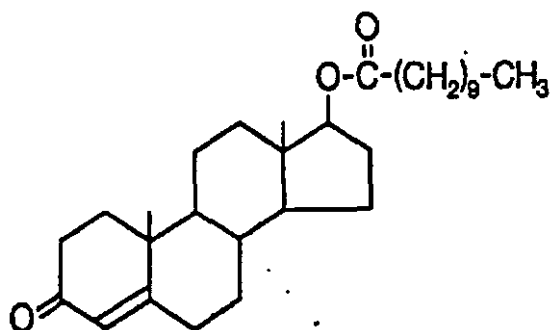
**Andriol** capsules should be taken after meals and swallowed without chewing.

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Testosterone undecanoate

17beta-undecanoyloxy-androst-4-en-3-one



Formula:  $C_{30}H_{48}O_3$

Molecular Weight: 456.7

Melting point: 63°C

Solubility:

in water - insoluble

in oleic acid -  $\geq 160$  mg/mL

Testosterone undecanoate is a creamy-white crystalline powder.

### Composition

Capsule contents: testosterone undecanoate, oleic acid

Capsule shell: Glycerol 85%, an aqueous solution of partially hydrogenated hydrolyzed starch (containing total solids consisting of 27-35% of sorbitol, 2-4% of mannitol and 61-71% of not hydrogenated hydrolyzed starch), sodium ethyl hydroxybenzoate, sodium propyl hydroxybenzoate, titanium dioxide, iron oxide red, gelatin

### Stability and Storage Recommendations

Storage conditions:

Pharmacist: refrigerated at 2° - 8°C. Protect from light and moisture. Do not freeze.

Patient: store between 15° and 25°C. Protect from light and moisture. Use within 90 days.

### AVAILABILITY

Each Andriol Capsule contains 40 mg of testosterone undecanoate in oleic acid. Each Andriol Capsule is an oval reddish-brown soft gelatin capsule marked **D<sub>3</sub>V**.

Andriol 40 mg is available in bottles of 60 and 100 capsules.



## INFORMATION FOR PATIENTS

**Andriol** (testosterone undecanoate) which has been prescribed to you by your doctor, is a testosterone preparation. Testosterone is a male hormone, an androgen, which is naturally produced in the body and necessary for the normal sexual development of males. Androgens are used to replace the hormone when the body is unable to produce enough on its own or to stimulate the beginning of puberty in certain boys. In addition, some of these medicines may be used for other conditions as determined by your doctor.

There is no good medical evidence to support the belief that the use of androgens in athletes will increase muscle strength. When used for this purpose, it may be dangerous to health because of unwanted effects such as too much fluid in the body and, liver disease; or swelling of breasts.

You should take Andriol only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

### Before Using This Medicine

In order to decide on the best treatment for your medical problem, your doctor should be told:

if you have ever had any unusual or allergic reaction to androgens or anabolic steroids.

if you are on a low-salt, low-sugar, or any other special diet, or if you are allergic to any substance, such as foods, sulfites or other preservatives, or dyes. Most medicines contain more than their active ingredient. Your doctor, nurse, or pharmacist can help you avoid products that may cause a problem.

if you are an adult male who plans to have children. High doses of androgens may cause infertility.



if you have any of the following medical problems:

- \*Breast cancer (in males)      \*Diabetes mellitus (sugar diabetes)
- \*Edema (swelling of face,      \*Prostate cancer  
hands, feet, or lower legs)      \*Liver disease
- \*Enlarged prostate      \*Heart or blood vessel disease
- \*Kidney disease

if you are now **taking any** other prescription or nonprescription (OTC) medicine, especially anticoagulants (blood thinners).

if you are bedridden.

How to store this medicine:

**Keep out of the reach of children.**

Store between 15° and 25°C. Protect from light and moisture. Use within 90 days.

Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

**Precautions While Using This Medicine**

Your doctor should check your progress at regular visits in order to make sure this medicine does not cause unwanted effects. Any male adolescent patient receiving androgens for delayed puberty should have bone development checked every six months.

Diabetics - This medicine may affect blood sugar levels. If you notice a change in the results of your urine sugar test or if you have any questions about this, check with your doctor.

**Side Effects of This Medicine**

Discuss these possible effects with your doctor:

Tumors of the liver, liver cancer, or peliosis hepatis, a form of liver disease, have occurred during long-term, high-dose therapy with androgens. Although these effects are rare, they can be very serious and may cause death.

When elderly male patients are treated with androgens, they may have an increased risk of enlarged prostate or cancer of the prostate.

Androgens may cause children to stop growing early or to develop too fast sexually. Radiographic examination of the hands and wrist should be performed every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects appear very often, when they do occur they may require medical attention.

**Check with your doctor immediately** if any of the following side effects occur:

- Yellow eyes or skin; flushing or redness of skin or any changes in skin color; skin rash or itching; hives
- Black, tarry, or tight-colored stools; dark-colored urine
- Purple or red-coloured spots on body or inside the mouth or nose
- Sore throat and/or fever
- Nausea or vomiting; vomiting of blood
- Abdominal or stomach pain (continuing); pain, tenderness, or swelling in the upper abdominal or stomach area
- Loss of appetite (continuing); unpleasant breath odor (continuing)
- Confusion; dizziness; headache (frequent or continuing); mental depression

- Feeling of discomfort (continuing)
- Shortness of breath
- Swelling of feet or lower legs
- Unusual bleeding; unusual tiredness
- Frequent or continuing erection; frequent urge to urinate
- Swelling of breasts or breast soreness

For elderly males only

- Difficult or frequent urination; unusual increase in sexual desire

Other side effects may occur which usually do not require medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

Constipation; diarrhea; stomach pain; trouble in sleeping; unusual decrease or increase in sexual desire

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

## PHARMACOLOGY

### Animal Pharmacology

In vitro and in **vivo** studies in rats indicated that testosterone undecanoate is not metabolized by gastric juices and is only slightly metabolized in the intestinal lumen. Studies also showed that testosterone undecanoate is metabolized to a lesser extent in the wall of the intestines during absorption than testosterone. Polar metabolites without the undecanoate side chain are absorbed

via the portal vein and unchanged testosterone undecanoate and the main metabolite, 5 alpha-dihydrotestosterone undecanoate are absorbed by way of the intestinal lymphatic system. It was found that testosterone undecanoate and **5alpha-dihydrotestosterone** undecanoate were present in plasma chylomicrons, absorbed by the lymphatic system and transported to the peripheral circulation. In this way, testosterone undecanoate does not undergo first-pass inactivation by the liver.

#### Human Pharmacokinetics

The active substance of Andriol, testosterone undecanoate, is well absorbed from the gastrointestinal tract. It is metabolized partly in the intestinal wall into **5** alpha-dihydrotestosterone undecanoate. Both testosterone undecanoate and the newly formed 5 alpha-dihydrotestosterone undecanoate are partly absorbed via the lymphatic system, circumventing first passage through the liver.

Administration of radioactively **labelled** testosterone undecanoate (**3-TU**) to men resulted in radioactivity in the lymph associated with unmetabolized testosterone undecanoate and 5 alpha-dihydrotestosterone undecanoate. Peak levels of radioactivity appeared in the lymph and plasma 2.5 - 5 hours after administration. The highest concentration of radioactivity in urine was found 2 hours later. During the first 24 hours approximately 40 % of the administered dose was found in urine and the total recovery of urine during the first week was **45-48%** (Fig. 1).

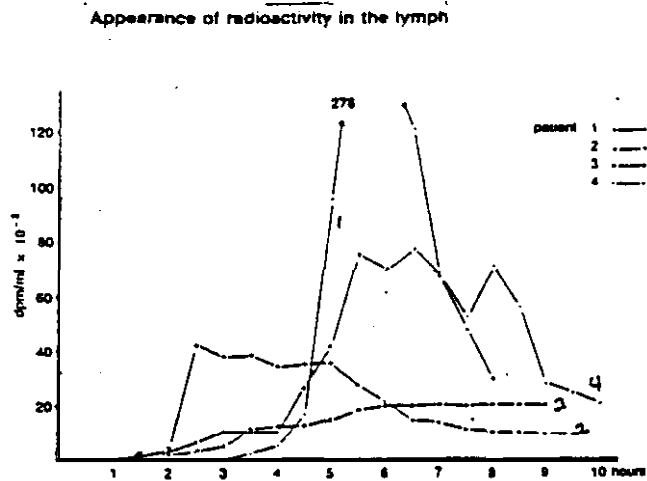
Absorption of testosterone undecanoate is increased when it is administered with a meal, since chylomicron production is stimulated producing increased absorption by the lymph (Fig. 2).

Peak serum levels can occur between 1 and 8 hours after oral ingestion of testosterone

undecanoate. In eugonadal men a doubling of plasma testosterone concentrations occurred 4 -5 hours after ingestion with a return to basal levels after approximately 10 hours.

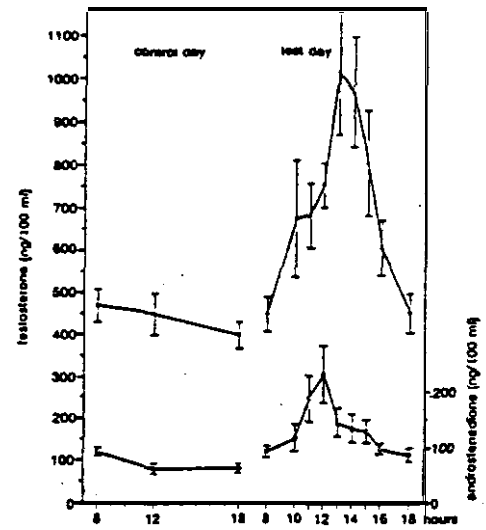
In general, the mean level of plasma testosterone appears to rise more slowly than that of 5 alpha-dihydrotestosterone and androstenedione in hypogonadal patients. The relatively slow increase in testosterone concentrations may be due to an increased testosterone clearance rate. Decreased SHBG concentrations and consequent decreased protein binding of testosterone has been observed which accounts for the increased levels of **free** and biologically active testosterone. Free testosterone is rapidly converted to 5 alpha-dihydrotestosterone, androstenedione, and **estradiol** (Table 1).

After administration of tritium-labelled testosterone undecanoate to healthy volunteers and hypogonadal men, approximately 85% of the radioactivity was excreted in 4 days, 70% in urine and 15% in **faeces**. The principal urinary **metabolites** were androsterone and etiocholanolone. Testosterone and 5 beta-androstane-3alpha-17beta-diol were also found. The relative quantities were similar to those found after intravenous administration of testosterone.



Appearance of radioactivity in the lymph after oral application of  $[3H]$ -TU dissolved in arachis oil. Patients 1 and 2 received the radioactive compound via a stomach tube, patient 3 in addition received 100 mg of unlabelled TU. Patient 4 swallowed 10 gelatin capsules containing the same amounts of labelled and unlabelled TU as received by patient 3.

Figure 1



Plasma testosterone and androstenedione in 8 men before and after oral administration of 100 mg TU in oil.

Figure 2

### Plasma T, 5 $\alpha$ -DHT and SHBG levels

plasma hormone	no treatment mean (SD)	placebo mean (SD)	TU 1st month mean (SD)	TU 2nd month mean (SD)
testosterone (pg/ml)	3071 (882)	2976 (732)	3777 (1540)	3558 (717)
DHT (pg/ml)	361 (47)	375 (69)	1083* (314)	1043** (223)
oestradiol (pg/ml)	49.6 (22.1)	31.1 (6.4)	46.5 (31.6)	38.3* (6.2)
SHBG (nmol/l)	3.26 (0.69)	2.7 (0.7)	1.68** (0.5)	1.72** (0.6)
LH (U/ml)	32.0 (6.2)	32.8 (12.2)	23.9 (7.4)	23.0** (11.2)
FSH (U/ml)	39.5 (4.6)	39.9 (6.9)	35.4* (6.3)	29.6* (12.5)

\*  $p < 0.05$

\*\*  $p < 0.01$

Effect of TU administration on plasma hormone levels of hypogonadal men suffering from Klinefelter's syndrome. Comparison of TU and a placebo.

Table 1

### Human pharmacology (Fig. 3 & 4, Table 2)

In healthy men daily oral doses of 160 mg/day for 14 days did not suppress plasma FSH and LH levels nor pituitary responsiveness to stimulation by LHRH.

In hypergonadotropic hypogonadal patients, testosterone undecanoate administration resulted in normalization of pituitary function, with FSH and LH being significantly reduced by testosterone undecanoate.

In hypogonadotropic hypogonadal patients, mean FSH and LH levels and pituitary responsiveness tended towards normalization.

### TOXICOLOGY

#### Acute Toxicity

	LD <sub>50</sub> mg/kg	
	oral	subcutaneous
mice	4000	2880
rat	4000	2880

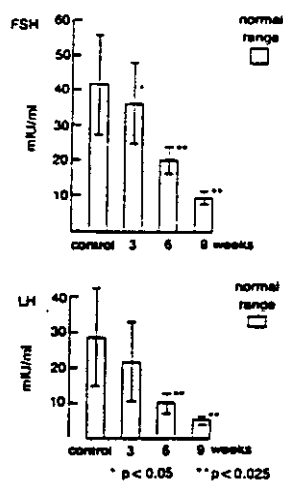
#### Repeated-dose studies

In rats given orally up to 80 mg/kg/day Andriol dissolved in oleic acid for 52 weeks, only systemic effects were seen that were attributable, directly or indirectly, to the known hormonal profile of androgens. These included:

- increased food consumption and body weight gain in females
- increased values relating to the red blood cell parameters in females
- increased kidney and prostate weights
- decreased pituitary, adrenal, testicular, epididymal and ovarian weights



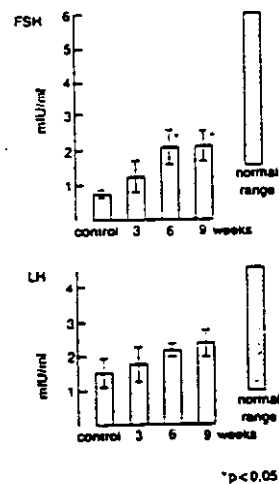
Testosterone undecanoate in hypogonadal males. Effect of TU administration in hypergonadotrophic patients



Mean ( $\pm$  SEM) plasma FSH and LH levels in hypergonadotrophic patients (n = 6).

Figure 3

Effect of TU administration in hypogonadotrophic patients



Mean ( $\pm$  SEM) plasma FSH and LH levels in hypogonadotrophic patients (n = 4).

Figure 4

LH and FSH cumulative response to 25  $\mu$ g of LH-RH i.v. in hypergonadotrophic (mean value and range) and hypogonadotrophic (individual values) hypogonadal patients

subjects	LH, mIU/90 min		FSH, mIU/90 min	
	pretreatment	at 9 weeks	pretreatment	at 9 weeks
hypergonadotrophic hypogonadal (n = 4)	3947 (907 - 4551)	1282 (571 - 1938)	2684 (948 - 3817)	436 (205 - 1040)
hypogonadotrophic hypogonadal (n = 2)	114 96	267 233	93 122	112 178
normal males (mean $\pm$ SD; n = 16)	410 $\pm$ 65		89 $\pm$ 37	

Table 2

- inhibition of spermatogenesis and ovarian activity
- increased uterine activity
- increased alkaline phosphatase values and increased hepatic weight in females

In dogs administered up to 80 **mg/kg/day** for 52 weeks orally, similar reversible hormonal changes occurred, except for increases in kidney and testicular weights. Kidney weight remained high during an 11-week period of withdrawal and spermiogenesis remained reduced in this group of dogs.

Although not observed at 26 weeks, a reversible increase in prostatic weight occurred by 52 weeks of drug administration.

#### Mutagenicity

Testosterone undecanoate was found to have no mutagenic activity in either the Ames Salmonella or rat micronucleus tests.

#### Carcinogenicity

Carcinogenicity testing of testosterone propionate in mice and rats by subcutaneous implantation has produced cervical-uterine tumours in female mice and prostatic adenocarcinomas in male rats. Hyperplastic epithelial lesions of the genital tract and an increased incidence of mammary tumours have resulted from neonatal treatment of female mice by subcutaneous injection of testosterone. **5 $\beta$ -dihydrotestosterone** also increased the incidence of mammary **tumours** in mice when given neonatally by **s.c.** injection.

### Reproductive Toxicity

Sexually mature male rats were given 5, 20 or 80 **mg/kg/day** of testosterone undecanoate or placebo orally for 9 weeks prior to and for 2 weeks during mating with untreated females.

The first generation (**F<sub>0</sub>**) males were subjected to further matings 3, 10 and 14 after cessation of treatment. Half the females were examined after 20 days of gestation while the remainder continued to term and reared their young to 28 days of age. Second generation (**F<sub>1</sub>**) males and females were selected and mating performance and fertility evaluated.

At 80 **mg/kg/day** impaired fertility occurred and increased pre-implantation loss (reduced litter size) in females mated with treated rats was recorded. This effect appeared to be reversible.

With the exception of a reduced post-weaning body weight of male progeny derived from the **final** mating, growth, development and fertility of offspring were similar in all groups. Autopsy of **F<sub>0</sub>** males 18 weeks after cessation of 80 **mg/kg/day** Andriol revealed a significant reduction in both absolute and relative testicular weights.

### Rabbit Liver Function

Rabbits were administered either placebo, testosterone undecanoate or methyltestosterone at a dose of 10 **mg/day** for 10 days and liver function assessed by evaluating BSP clearance and plasma SGOT and SGPT activity. Testosterone undecanoate did not adversely affect liver function (Table 3).

Effects of Orally Administered Testosterone Undecanoate (TU) and  
Methyltestosterone (MeT) (10 mg/kg/day for 10 days) in Liver  
Function Test in Rabbits  
(mean  $\pm$  SE)

	<u>B S P (10mcg/mL plasma)</u>				
	<u>5</u> <u>minutes+</u>	<u>10</u> <u>minutes+</u>	<u>20</u> <u>minutes+</u>	<u>SGOT</u> <u>(Karmen</u> <u>Units/mL)</u>	<u>SGPT</u> <u>(Karmen</u> <u>Units/mL)</u>
Control (placebo tablets)	81 $\pm$ 12	33 $\pm$ 5	9 $\pm$ 1	10 $\pm$ 1	24 $\pm$ 2
TU	106 $\pm$ 9	35 $\pm$ 5	7 $\pm$ 1	11 $\pm$ 1	25 $\pm$ 3
MeT	161 $\pm$ 25*	76 $\pm$ 13*	19 $\pm$ 4*	52 $\pm$ 9*	60 $\pm$ 13*
BSP:	Sulphobromophthalein				
SGOT:	serum glutamic oxaloacetic transaminase				
SGPT:	serum glutamic pyruvic transaminase				
+: *.	after administration of BSP (15 mg/kg) statically significant				

Table 3

### CLINICAL TRIALS

Several studies have demonstrated the efficacy of Andriol in replacement therapy in male hypogonadal disorders.

Testosterone undecanoate showed a significant effect on sexual activity, ejaculation and subjective quality of sexual acts during a controlled study involving 12 hyper- and **hypo-gonadotrophic** men. Patients received 160 mg/day of Andriol or placebo in a double-blind crossover fashion for 2 months (Table 4).

A similar study involving 4 **Klinefelter** patients produced a significant increase in sexual thoughts, associated feelings of excitement and number of total sexual acts during testosterone

undecanoate administration as compared to placebo. However, no significant effect was produced on self-reported mood or energy, nor in erectile responsiveness measured in the laboratory (Fig. 5 & Table 5).

The efficacy of a 120 **mg/day** dose of Andriol compared to that of a 1.50 **mg/day** dose of mesterolone has been studied in a double-blind, randomised trial with respect to libido, sexual performance and mental state. Andriol rated significantly better on all parameters (Fig. 6,7,8, & 9).

The effects of Andriol administered for 12 weeks at 120 **mg/day** was studied in males suffering from infertility related to low or sub-normal sperm counts with a relatively high number of pathological spermatozoa. Andriol treatment significantly improved sperm morphology, markedly increased sperm density in males with a density of less than 20 million per ml ejaculate, and significantly reduced the number of pathological spermatozoa with head- or tail-deformities in patients with a sperm density ranging from 20.1 to 40 million/ml. Testosterone levels increased as a consequence of Andriol administration while FSH decreased (Tables 6 & 7).

Of 12 pre-pubertal agonadal boys receiving 60 **mg/day** of testosterone undecanoate for 18 to 24 months, all, except one, showed signs associated with progressive sexual maturation. During treatment, plasma testosterone and androstenedione levels significantly increased whereas LH and FSH plasma levels did not (Fig. 10 & 11).

The effectiveness of Andriol in aging men (53-62 years) with low androgen levels, vasomotor symptoms, sexual impotence, and psychic changes has been assessed following treatment with 50 **mg/day** for an 8 month period. Mean plasma testosterone levels rose during and after Andriol therapy, but did not attain the normal range. Plasma dihydrotestosterone and  $E_2$  levels also rose,

followed by a decline in the post-treatment period. Mean FSH and LH plasma levels decreased although they remained above the upper normal limit. All patients experienced improvement in sexual activities and libido over the 8 month study period with no side effects nor change in the prostate gland reported.

Andriol has proved to be a suitable and effective therapy for hypogonadal patients, improving sexual performance, libido and mental state. Andriol has been shown to be well tolerated with only a few, mild side-effects, mainly of gastro-intestinal origin.

Andriol in a dose of 50-200 **mg/day** has been proven to be a safe way of treating androgen deficiency in a long-term study involving 35 men receiving testosterone undecanoate for 72 months. Preliminary evidence suggests that it does not effect liver function nor induce BHP or gynecomastia (Table 8).

Effect of TU on sexual interest and behaviour

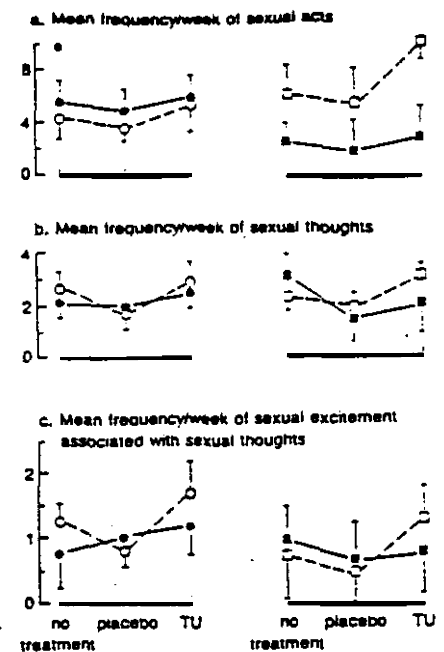
(hypo n=5; hyper n=6; all n=11)	diagnostic group	no treatment mean (SD)	placebo mean (SD)	TU Mean (SD)	TU v. placebo (one-tail)
no. of sexual acts (per week)	hypo	0.9 (0.8)	0.9 (0.9)	2.6 (1.2)	<0.05
	hyper	0.7 (0.7)	0.5 (0.8)	1.8 (0.9)	<0.025
	all	0.8 (0.7)	0.7 (0.9)	2.1 (1.2)	<0.005
no. of ejaculations (per week)	hypo	0.4 (0.8)	0.4 (0.9)	2.3 (1.0)	<0.05
	hyper	0.3 (0.3)	0.1 (0.1)	1.3 (0.3)	<0.025
	all	0.3 (0.6)	0.2 (0.6)	1.7 (0.9)	<0.005
subjective quality of sexual acts (mean per act)	hypo	3.0 (0.8)	3.4 (0.9)	3.5 (0.6)	*
	hyper	2.6 (1.2)	2.4 (0.6)	3.3 (0.7)	*
	all	2.8 (1.0) n=9	3.0 (0.9) n=6	3.4 (0.5) n=11	NS
frequency of sexual thoughts (per week) (0-4)	hypo	1.7 (0.9)	1.5 (1.0)	2.7 (0.9)	<0.05
	hyper	1.4 (0.5)	1.3 (0.6)	2.3 (0.6)	<0.05
	all	1.5 (0.7)	1.4 (0.8)	2.5 (0.7)	<0.005
frequency of sexual excitement (0-2)	hypo	0.7 (0.4)	0.6 (0.6)	1.4 (0.2)	<0.05
	hyper	0.4 (0.3)	0.4 (0.3)	1.0 (0.4)	<0.05
	all	0.5 (0.3)	0.5 (0.5)	1.2 (0.4)	<0.005

\* Too few differences to test.

Comparison of testosterone undecanoate and placebo effects on sexual interest and behaviour (self-ratings).

Table 4

Effect of TU in Klinefelter patients



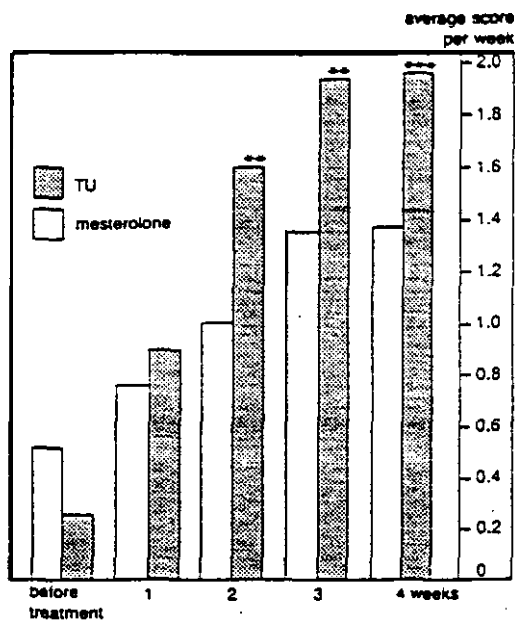
Patients 2 (•) and 4 (■) received: no treatment, placebo, TU treatment  
Patients 1 (•) and 3 (□) received: no treatment, TU treatment, placebo

Figure 5

Effects of testosterone undecanoate on sexual activity, ejaculation and frequency of sexual thoughts

	NO treatment (NT) Mean (SD)	Placebo (PI) Mean (SD)	Testosterone undecanoate (TU) Mean (SD)	Statistical difference (I test, one tail)
Sexual acts/ week	4.5 (1.4)	3.9 (1.3)	5.9 (2.6)	PI v. TU; $P < 0.10$ NT v. PI; $P < 0.01$ NT v. TU; NS
Ejaculations/ week	2.6 (0.5)	2.3 (0.8)	3.8 (1.8)	NS
Frequency of sexual thoughts (scale 0-4 week)	2.5 (0.4)	1.8 (0.1)	2.6 (0.5)	PI v. TU; $P < 0.025$ NT v. PI; $P < 0.05$ NT v. TU; NS
Sexual excitement associated with thoughts (scale 0-2/week)	1.0 (0.2)	0.8 (0.2)	1.3 (0.4)	PI v. TU; $P = 0.05$ NT v. PI; NS NT v. TU; NS

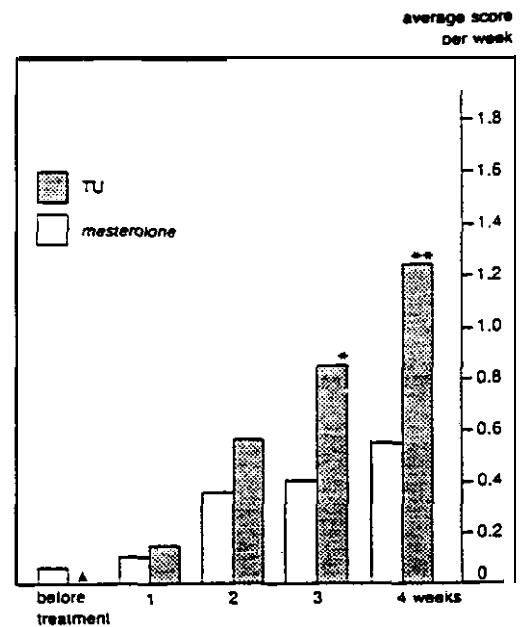
Table 5



Average weekly scores of libido. Statistically significant difference as compared with mesterolone: \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Figure 6

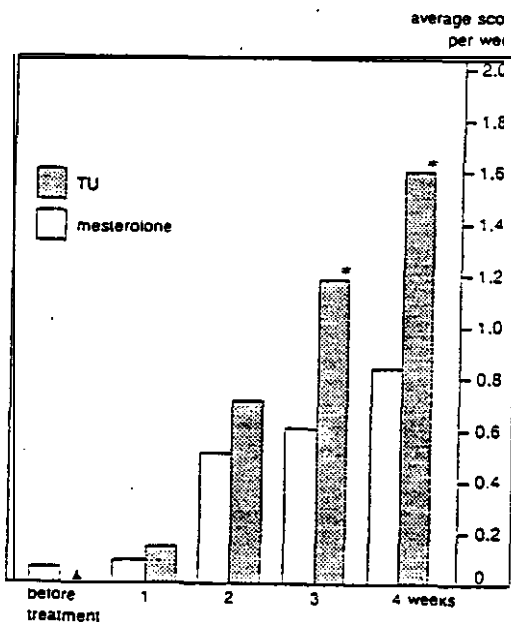
### Effect of TU on erections



Average weekly scores of erections. Statistically significant difference as compared with mesterolone:  $p < 0.05$ , \*\*  $p < 0.01$ ,  $\Delta$  TU score is 0.

Figure 7

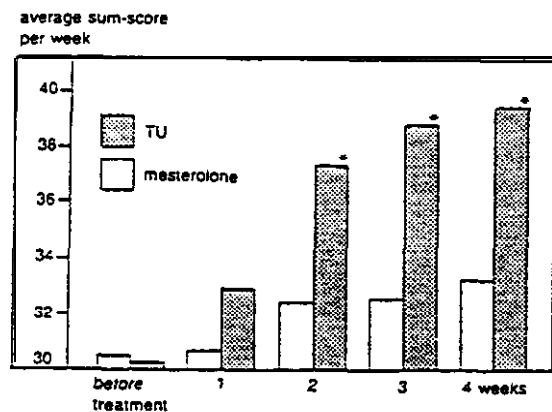
### Effect of TU on ejaculations



Average weekly scores of ejaculations during intercourse or attempted intercourse. \* Statistically significant difference ( $p < 0.001$ ) as compared with mesterolone.  $\Delta$  TU score is 0.

Figure 8

### Effect of TU on mental state



Average weekly scores of mental state. \* Statistically significant difference ( $p < 0.05$ ) as compared with mesterolone.

Figure 9



Evaluation of the effects of TU treatment in infertile men: a comparison with placebo. Results of testing changes after treatment against zero.

all patients: variable	Placebo	Verum
sp. density	—	$p < 0.0161$
% path. forms	—	$p < 0.0471$
group A: variable	Placebo	Verum
sp. density	—	$p < 0.0393$
% path. forms	$p < 0.0231$	—
group B: variable	Placebo	Verum
sp. density	—	—
% path. forms	—	$p < 0.0002$
tail defects	—	$p < 0.0169$
progr. motile sp.	—	$p < 0.0145$

Table 6

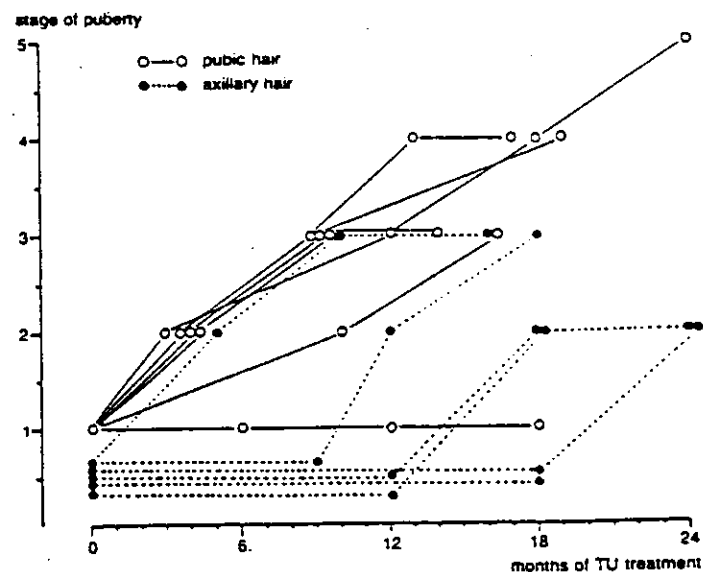
Results of TU and placebo treatment in patients with oligozoospermia

variable	all cases (n=57)	group A (n=28)	group B (n=29)	
% normal forms	—	$p < 0.05$	$p < 0.01$	$P < V$
% path. forms	—	$p < 0.05$	$p < 0.01$	$P > V$
head deformations	—	—	$p < 0.05$	$P > V$
total testosterone	$p < 0.05$	—	—	—
FSH	—	$p < 0.05$	—	$P > V$
LH	$p < 0.05$	$p < 0.05$	—	$P > V$

Differences between pre- and posttreatment values are calculated and then tested for significances between placebo (P) and TU = verum (V).

Table 7

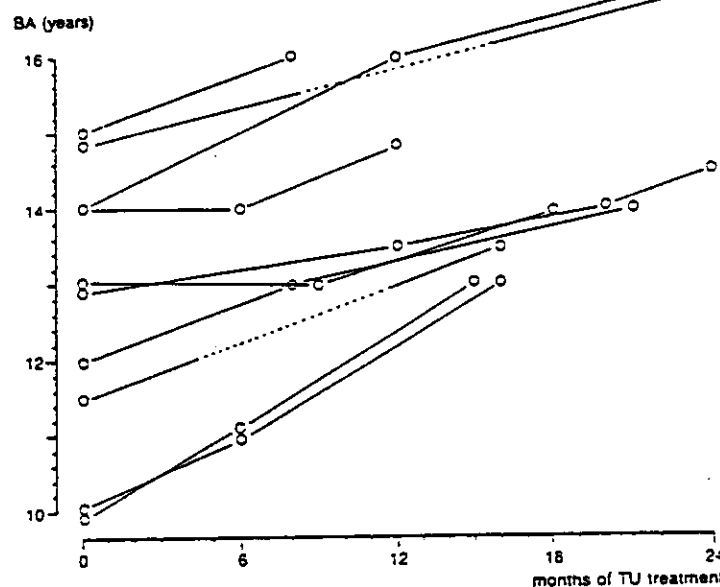
# Effect on hair growth of agonadal boys



Development of pubic and axillary hair in agonadal boys (n=6, not treated with androgens previously) during treatment with an average dose 60 mg TU.

Figure 10

# Effect on bone development of agonadal boys



Development of bone age (BA) in agonadal boys (n=10) during treatment with an average dose of 60 mg TU.

Figure 11

Liver function tests in 35 men taking SO-200mg testosterone undecanoate (TU)/day in a 72 month follow-up study. Values are the mean  $\pm$  SD

Parameter	Reference range	Months after start of TU					
		12	24	36	48	60	72
bilirubin (umol/l)	<9	<9	<9	<9	<9	<9	<9
Alkaline phosphatase (U/l)	<100	75 $\pm$ 12	74 $\pm$ 13	78 $\pm$ 11	71 $\pm$ 14	75 $\pm$ 13	74 $\pm$ 13
$\gamma$ -glutamyltransferase (U/l)	<30	15 $\pm$ 4	18 $\pm$ 4	13 $\pm$ 7	15 $\pm$ 6	13 $\pm$ 7	16 $\pm$ 6
SGOT (AST)(U/l)	5-15	8 $\pm$ 2	8 $\pm$ 3	9 $\pm$ 3	10 $\pm$ 3	9 $\pm$ 2	8 $\pm$ 3
SGPT (ALT)(U/l)	5-15	9 $\pm$ 2	10 $\pm$ 2	9 $\pm$ 3	9 $\pm$ 3	10 $\pm$ 2	9 $\pm$ 3
LDH (U/l)	<175	118 $\pm$ 20	112 $\pm$ 21	115 $\pm$ 27	128 $\pm$ 21	125 $\pm$ 22	110 $\pm$ 23
$\alpha$ -foetoprotein (pg/l)	<50	<50	<50	<50	<50	<50	<50
Thrombotest (sec)	44-55	47 $\pm$ 1.2	46 $\pm$ 1.5	46 $\pm$ 1.6	46 $\pm$ 1.6	46 $\pm$ 1.5	47 $\pm$ 1.5
Kaolin-cephalin (sec)	46-50	48 $\pm$ 1.2	46 $\pm$ 1.4	46 $\pm$ 1.5	47 $\pm$ 1.4	47 $\pm$ 1.4	48 $\pm$ 1.2
Acid phosphatase (U/l)	<10	<10	<10	<10	<10	<10	<10
Testosterone (nmol/l)	a24	5.4 $\pm$ 1.9		6.0 $\pm$ 2.0		6.1 $\pm$ 1.8	5.9 $\pm$ 1.7
Oestradiol-17 $\beta$ (nmol/l)	0.04-0.12	0.14 $\pm$ 0.08		0.13 $\pm$ 0.09		0.14 $\pm$ 0.09	0.12 $\pm$ 0.09
Dihydrotestosterone (nmol)	0.8-2.5	3.5 $\pm$ 1.2		3.4 $\pm$ 1.3		3.2 $\pm$ 1.4	3.3 $\pm$ 1.3

Table 8

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