PRODUCT MONOGRAPH

CYPROTERONE

Cyproterone Acetate Tablets BP

50 mg

Antiandrogen

AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

DATE OF REVISION:
July 1, 2010

PRODUCT MONOGRAPH

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Cyproterone Acetate Tablets BP
50 mg

THERAPEUTIC CLASSIFICATION

Antiandrogen

ACTIONS AND CLINICAL PHARMACOLOGY

Cyproterone acetate is a steroid which clinically demonstrates two distinct properties:

a) Antiandrogenic: Cyproterone acetate blocks the binding of dihydrotestosterone - the active metabolite of testosterone to the specific receptors in the prostatic carcinoma cell.

b) Progestogenic/antigonadotrophic: Cyproterone acetate exerts a negative feedback on the hypothalamo-pituitary axis, by inhibiting the secretion of LH leading to diminished production of testicular testosterone.

The absorption of cyproterone acetate following oral administration is complete. Peak plasma levels are reached 3 - 4 hours after administration. Plasma levels fall rapidly during the first 24 hours as a result of tissue distribution and excretion, and plasma half-life was 38 ± 5 hours.

Most of the cyproterone acetate is excreted unchanged in the feces (60%) or urine (33%) within 72 hours.

Cyproterone acetate is eliminated with the urine mainly in the form of unconjugated metabolites and with the bile (feces) in the form of glucuronidized metabolites.

The principal metabolite identified was 15β-hydroxy-cyproterone acetate.

Comparative Bioavailability

A standard, randomized, two-way crossover study was conducted in 18 healthy, adult, male volunteers to evaluate the relative bioavailability of single oral doses of CYPROTERONE 50 mg Tablets and Androcur® 50 mg Tablets. The mean pharmacokinetic parameters of these subjects are summarized in the following table.

Summary Table of the Comparative Bioavailability Data
Cyproterone Acetate (Dose: 1 x 50 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	CYPROTERONE 50 mg Tablets	ANDROCUR®† 50 mg Tablets	
AUC_{0-72}(ng·h/mL)	1966.3023 2010.819 (21)	2108.7500 2148.491 (18)	93.2%
AUC_I (ng·h/mL)	2566.5294 2662.606 (27)	2724.9591 2806.800 (24)	94.2%
C_{MAX} (ng/mL)	103.1616 106.854 (31)	128.6780 134.074 (28)	80.2%
T_{MAX}* (h)	3.02 (61)	2.50 (32)	--
$T_{½}$* (h)	37.60 (31)	38.21 (26)	--

* Arithmetic means (CV%); ** Based on the least squares estimate;
† Androcur® is manufactured by Berlex Canada Inc. and was purchased in Canada.

INDICATIONS AND CLINICAL USE

CYPROTERONE (cyproterone acetate) is indicated for the palliative treatment of patients with advanced prostatic carcinoma.

CONTRAINDICATIONS

- Known hypersensitivity to the drug.
- Active liver disease and hepatic dysfunction.
- Renal insufficiency.

WARNINGS

Liver Function

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 - 300 mg cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops usually, several months after treatment has begun. Liver function tests should be performed before treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

Inhibition of Spermatogenesis

The sperm count and the volume of ejaculate are reduced at oral doses of 50 - 300 mg per day. Infertility is usual, and there may be azoospermia after 8 weeks of therapy, which is associated with atrophy of seminiferous tubules.

Follow-up examinations on discontinuation of therapy have shown these changes to be reversible. Spermatogenesis usually reverts to its previous level about 3 - 5 months after stopping cyproterone acetate, or in some patients, after up to 20 months. Production of abnormal spermatozoa during cyproterone acetate therapy has been observed; their relationship to abnormal fertilization or malformed embryos is not known.

Gynecomastia

Benign nodules (hyperplasia) of the breast have been reported; these generally subside 1 - 3 months after discontinuation of therapy and/or after a reduction of dosage. The reduction of dosage should be weighed against the risk of inadequate tumour control.

Depression

Cyproterone acetate therapy has occasionally been associated with an increased incidence of depressive mood changes, especially during the first 6 - 8 weeks of therapy. Similar mood changes have also been seen following surgical castration and are considered to be due to androgen deprivation. Patients with tendencies to depressive reaction should be carefully observed.

PRECAUTIONS

Thromboembolism

Clinical investigations have shown that when cyproterone acetate is used alone, it has minor effect on blood clotting factors. However, when cyproterone acetate was combined with ethinyl estradiol, changes were found in increased coagulation capability. There is an inherent risk for those patients with a history of thrombophlebitis or thromboembolism for recurrence of the disease. Cyproterone acetate should be discontinued at the first sign of thrombophlebitis or thromboembolism and the patient should be carefully re-evaluated if manifestations of thrombotic disorders (thrombo-phlebitis, cerebrovascular complications, retinal thrombosis or pulmonary embolism) occur.

Adrenocortical Function

Suppression of adrenocortical function tests have occurred in patients receiving high doses (100 mg/ m^2) of cyproterone acetate.

Reduced response to endogenous ACTH was noted by the Metyrapone test; furthermore, reduced ACTH and cortisol blood levels, determined by the Mattingly method were also found.

It is therefore recommended that adrenocortical function be monitored periodically by serum cortisol assay.

Diabetes

Cyproterone acetate may impair carbohydrate metabolism. Parameters of carbohydrate metabolism, fasting blood glucose and glucose tolerance test, should be examined carefully in all patients and particularly in all diabetics before and regularly during therapy with cyproterone acetate.

Hematology

Hypochromic anemia has been observed rarely during therapy with cyproterone acetate. Regular hematological assessment is recommended.

Nitrogen Balance

A negative nitrogen balance is usual at the start of therapy, but does generally correct itself within 3 months of continued therapy.

Metabolic Effects

Fluid retention, hypercalcemia and changes in the plasma lipid profile may occur. Accordingly, cyproterone acetate should be used with caution in patients with cardiac disease.

Skin

Cyproterone acetate therapy may cause a reduction of sebum production leading to dryness of the skin, and transient patchy loss of body hair.

Concomitant Alcohol

Alcohol may reduce the antiandrogenic effect of cyproterone acetate in hypersexuality. The relevance of this in prostatic carcinoma is not known; however, it would be prudent to inform the patients that the use of alcohol during cyproterone acetate therapy is not advisable.

Physical Performance

Patients should be informed that fatigue and lassitude are common in the first few weeks of therapy, but usually becomes much less pronounced from the third month on.

Marked lassitude and asthenia necessitate special care when driving or operating machinery.

ADVERSE REACTIONS

The adverse events associated most frequently with the use of cyproterone acetate are those related to the hormonal effects of the drug. These reactions usually disappear upon discontinuation of therapy or reduction of dose:

> increased libido, breast enlargement, breast tenderness, benign nodular hyperplasia of the breast, galactorrhea, gynecomastia, abnormal spermatozoa, impotence, inhibition of spermatogenesis.

Other adverse events which have been reported are listed below:

Cardiovascular System

Hypotension, tachycardia, heart failure, syncope, myocardial infarct, hemorrhage, cerebrovascular accident, cardio-vascular disorder, retinal vascular disorder, embolus, pulmonary embolism,

superficial and deep thrombophlebitis, thrombosis, retinal vein thrombosis, phlebitis, vascular headache, shock.

Gastrointestinal System

Constipation, diarrhea, indigestion, anorexia, nausea, vomiting, chole-static jaundice, cirrhosis of liver, hepatic coma, hepatitis, hepatoma, hepatomegaly, jaundice, liver carcinoma, liver failure, abnormal liver function test, liver necrosis, pancreatitis, glossitis.

Hematology

Increased fibrinogen, decreased prothrombin, thrombocytopenia, anemia, hemolytic anemia, hypochromic anemia, normocytic anemia, leukopenia, leukocytosis.

Metabolism

Negative nitrogen balance, decreased response to ACTH, hyperglycemia, lowered cortisol, hypercalcemia, increased SGOT, increased SGPT, increased creatinine, hypernatremia, edema, weight gain, weight loss, diabetes mellitus.

Musculoskeletal System

Myasthenia, osteoporosis.

Nervous System

Fatigue, lassitude, weakness, hot flashes, increased sweating, aphasia, coma, depression, dizziness, encephalopathy, hemiplegia, personality disorder, psychotic depression, abnormal gait, headache.

Respiratory System

Asthma, increased cough, dyspnea, hyperventilation, respiratory disorder, shortness of breath on effort, lung fibrosis.

Skin

Eczema, urticaria, erythema nodosum, exfoliative dermatitis, rash, maculopapular rash, dryness of the skin, pruritis, alopecia, hirsutism, skin discolouration, photosensitivity reactions, scleroderma.

Sensory System

Ear disorder, optic atrophy, optic neuritis, abnormality of accommodation, abnormal vision, blindness, retinal disorder.

Urogenital System

Enlarged uterine fibroids, uterine hemorrhage, increased urinary frequency, bladder carcinoma, kidney failure, hematuria, urate crystalluria, urine abnormality.

Other

Ascites, allergic reaction, asthenia, chills, fetal chromosome abnormality, death, fever, hernia, malaise, injection site reaction.

Adverse reactions are rarely of sufficient severity to require dosage reduction or discontinuation of treatment.

If reactions are severe, it may be beneficial to reduce the dosage.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of fatal overdosage in man with cyproterone acetate. There are no specific antidotes and treatment should be symptomatic. If oral overdosage is discovered within two to three hours, gastric lavage can safely be used if indicated.

DOSAGE AND ADMINISTRATION

Oral Tablets

The usual daily initial and maintenance dose of CYPROTERONE (cyproterone acetate) is 4 - 6 tablets (200-300 mg) divided into 2 - 3 doses and taken after meals.

After orchiectomy a lower daily dose of 2 - 4 tablets (100-200 mg) is recommended.

CYPROTERONE therapy should not be discontinued when remission or improvement occurs.

The dosage may be reduced if side effects are intolerable, but should be kept within the oral range of 2 - 6 tablets daily (100-300 mg).

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

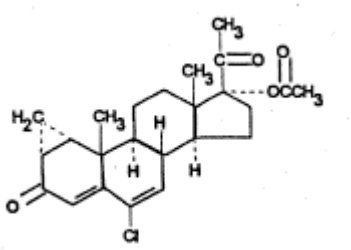
Proper Name: Cyproterone acetate

Chemical Names:

1) 3′*H*-Cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione, 17-(acetyloxy)-6-chloro-1,2-dihydro-, (1β,2β)-;

2) 6-Chloro-1β,2β-dihydro-17-hydroxy-3′*H*-cyclopropa[1,2]-pregna-1,4,6-triene-3,20-dione acetate.

Structural Formula:



Molecular Formula: $C_{24}H_{29}ClO_4$

Molecular Weight: 416.94

Description:

White or almost white, odourless, crystalline powder. Insoluble in water, very soluble in chloroform, freely soluble in acetone and soluble in methanol. Melting point is about 210°C.

COMPOSITION

CYPROTERONE (cyproterone acetate) Tablets BP contain 50 mg of cyproterone acetate. CYPROTERONE Tablets also contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium and magnesium stearate.

STABILITY AND STORAGE CONDITIONS

CYPROTERONE Tablets should be stored at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

CYPROTERONE (cyproterone acetate) 50 mg tablets BP are off-white, round, flat-faced tablets with bevelled-edges, embossed "CYP" over "50" scored on one side.

CYPROTERONE Tablets are available in bottles of 100, and unit dose packages of 60 and 100 tablets.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Antiandrogenic Effects

Cyproterone acetate at doses of 10 or 50 mg/kg inhibits the effects of endogenously produced and exogenously administered androgens at the prostate by means of competitive inhibition.

In mice and dogs, cyproterone acetate induces a dose-dependent atrophy of the accessory sex glands, the prostate, seminal vesicles and preputial glands.

Spermatogenesis is inhibited in a dose-related manner; however, the atrophy in the Leydig cells are slight.

In the rat, the start of puberty is prevented or delayed. Cyproterone acetate inhibits the physiological closure of the epiphyseal cartilages and bone maturation.

It impairs the function of the sebaceous glands, and the thickness of the epidermis decreases.

The treatment of pregnant animals with cyproterone acetate leads to developmental disturbances in male fetuses. Testosterone-dependent differentiation processes are affected: signs of feminization of varying degrees of severity develop.

Progestogenic and Antigonadotrophic Effect

On subcutaneous injections a total dose of 0.003 mg, cyproterone acetate is about 100 times stronger than progesterone in the maintenance of pregnancy (Clauberg test). Like all potent progestogens, cyproterone acetate has antigonadotrophic properties which can be demonstrated in the parabiosis test, the testicular inhibition test in infantile rats and by the inhibition of ovulation.

CLINICAL PHARMACOLOGY

Antiandrogenic Effect

The following actions, which are associated with the antiandrogenic effects, have been described in man:

· Reduction of sexual drive;
· Inhibition of spermatogenesis;
· Palliative effect in prostatic carcinoma;
· Inhibition of sebaceous gland activity;

· Suppression of signs of androgenization in women;
· Inhibition of premature genital development in children and other associated symptoms.

Progestogenic and Antigonadotrophic Effect

Cyproterone acetate in man is also a potent progestogen and has an antigonadotrophic effect. It intervenes with the hypothalamo-pituitary pathway, causing an inhibition of increased secretion of LH, and a decrease in gonadal testicular androgens. Thus, unlike pure antiandrogens, cyproterone acetate does not cause a compensatory increase in androgen secretion.

Other Endocrine Effects

No distinct influence on the 17-ketosteroids, 17-ketogenic steroids or on total estrogens in the 24-hour urine has been observed in male patients. On fluorometric determination of urinary cortisol, the value apparently increases because the cyproterone acetate eliminated with the urine is also measured. Simultaneously, cyproterone acetate also reduces the reaction of the adrenal cortex to exogenous ACTH in patients; the baseline cortisol and ACTH values may also be reduced.

Pharmacokinetic Studies in Animals

Pharmacokinetic studies have been carried out in a number of animal species (rats, rabbits, dogs and monkeys) using either methylene-^{14}C or carboxy-^{14}C-labelled cyproterone acetate.

Cyproterone acetate is absorbed at most dose levels tested except in high doses. Peak plasma levels are usually obtained within 1 - 4 hours of oral dosing. Because of its lipophilic character, cyproterone acetate is taken up and concentrated in the liver and fatty tissues in all animal species. Cyproterone acetate is not hydrolyzed, and mainly cyproterone acetate and the metabolite 15β-hydroxy-cyproterone acetate are found in the tissues and in plasma. The elimination half-life of cyproterone acetate is slow in most species (1-2 days), in a ratio of 4:6 with urine and feces; an exception is the dog, which excretes cyproterone acetate in 1 - 3 days. On repeated daily dosing, cyproterone acetate shows limited rise and plasma levels can be taken as a reliable index of the concentrations of cyproterone acetate in the body. Cyproterone acetate passes the placental barrier but only reaches the fetus in low concentrations. The pharmacokinetics and biotrans-formation and metabolic spectra of cyproterone acetate are similar in man and the rhesus monkey.

Human Pharmacokinetic Studies

A bioavailability study was performed in 5 male volunteer subjects receiving a single oral dose of 50 mg ^{14}C-cyproterone acetate tablets.

Results of the study showed that cyproterone acetate is absorbed slowly, but completely (100%) from the gastrointestinal tract. The maximum plasma level was reached 3 to 4 hours after ingestion. The mean plasma levels were 700 nmol (290 μg/L) cyproterone acetate or, including the radio-activity of metabolites, 960 nmol (400 μg/L) cyproterone acetate equivalent.

The plasma levels fell quickly up to 24 hours after administration because of extensive tissue distribution. The half-life of cyproterone acetate in plasma was calculated as 38 ± 5 hours (see Figure 1).

On oral administration cyproterone acetate was eliminated with a half-life of 38 ± 2 hours. After 10 days, 33 ± 6% of the dose could be recovered in the urine and 60 ± 8% in the feces (see Figure 2).

Figure 1
Relationship of unchanged cyproterone acetate to the total ^{14}C-labelled substance (cyproterone acetate + metabolites) in the plasma of a male subject following oral administration of 50 mg ^{14}C-cyproterone acetate

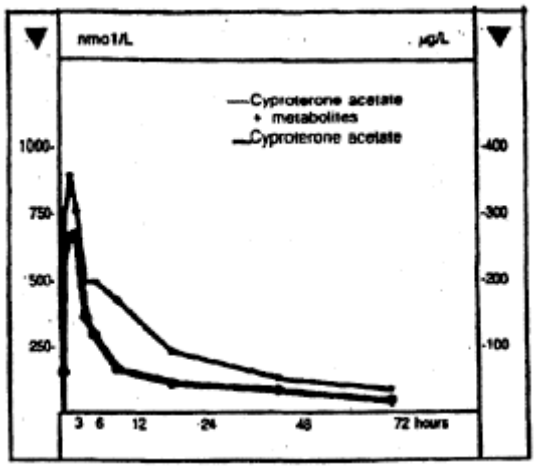
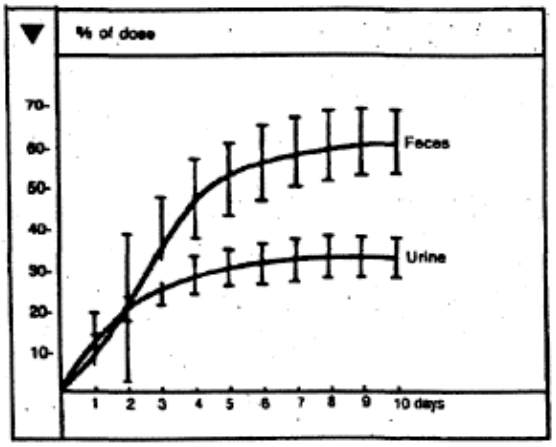


Figure 2
Elimination (% of dose) following oral administration of 50 mg ^{14}C-cyproterone acetate in male subjects.

Mean values ± standard deviation (n=5)



TOXICOLOGY

Cyproterone acetate has been found at low doses of 2-10 mg/kg to cause liver abnormalities in dogs and rats in the form of proliferative liver changes including increased liver weight, liver cell hypertrophy with an increase in the smooth endoplasmic reticulum and a rise in the serum glutamic pyruvic transaminase (SGPT). At high doses of 50-100 mg/kg, nodular hepatic hyperplasia and hepatomas have also been observed.

Recognized first-line tests of genotoxicity gave negative results when conducted with CPA. However, further tests showed that CPA was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for CPA. One *in vivo* consequence of CPA treatment was the increased incidence of focal, possible pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats.

The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

Acute Toxicity Studies

The LD_{50} after single application of cyproterone acetate was as follows:

Animal Species	Oral (mg/kg)	Subcutaneous (mg/kg)	Intraperitoneal (mg/kg)	Intramuscular (mg/kg)
Mouse	>6000	>5000	>4000	--
Rat	>4000	1500	1000	--
Dog	>3000	---	---	>100 (approx.)

On the basis of the above LD_{50} values, cyproterone acetate can be considered practically non-toxic following single dose administration. The maximum intramuscular doses were also tolerated without symptoms in the dog, with exception of local tolerance manifestation.

Chronic Toxicity Studies

Animal Species	Dosage and Duration	Mortality and Clinical and Laboratory Observations	Necropsy and Histopathology
Rats 35/sex/dose	0, 10, 50 and 250 mg/kg 78 weeks oral	250 mg/kg: Marked increase in mortality rate. 50 and 250 mg/kg: 40-50% decrease in body weight gain. SGPT increase: Males 10 and 250 mg/kg; females 50 mg/kg. BUN increase: Males 50 and 250 mg/kg. Cholesterol: All treated groups.	Dose related increase in liver weights. Increase thyroid weight except for low dose males. Dose related decrease in gonads, adrenal, prostate, seminal vesicle and uterus weights. Histopathology: Toxic manifestation in liver and kidneys - less at 10 mg/kg, more extensive at 50 and 250 mg/kg. Changes included: yellow nodules and mottling of liver (including liver cell hyperplasia and liver cell adenomas and endoplasmic inclusion bodies), discoloured kidneys with rough surfaces.

Animal Species	Dosage and Duration	Mortality and Clinical and Laboratory Observations	Necropsy and Histopathology
Rats 60/sex/dose	0, 0.04, 0.4 and 2 mg/kg 104 weeks oral	No drug related mortality. Dose related decrease in body weight gains in males and increase in females. Food consumption reduced and thinning and loss of hair was also noted for high dose males. Decrease in hemoglobin and erythrocytes at 0.4 and 2 mg/kg. SGOT, SGPT and alkaline phosphatase increased at 2 mg/kg.	2 mg/kg increased incidence of subcutaneous masses and/or nodules; liver discolouration and nodules; atrophy of testes, seminal vesicles and prostate. Increased incidence of mammary neoplasms (adenomas and adenocarcinomas).
Mice 50/sex/dose	0, 0.04, 0.4 and 2 mg/kg 105 weeks oral	No dose related mortality. Thinning and loss of hair at 2 mg/kg. Slightly reduced body weight gain at 2 mg/kg.	Slightly increased incidence of skin masses and/or nodules and alopecia. No drug related inflammatory, degenerative, proliferative and/or neoplastic lesions.
Dogs Beagle 4/sex/dose	0, 10, 32 and 100 mg/kg 55 weeks oral	No mortality. Excessive lacrimation, retarded pupillary reflex, mild conjunctivitis, hyperemia of gums, abdominal distention, sparsity of hair, and quieted behaviour. Laboratory tests: Slightly elevated alkaline phosphatase and SGPT at 100 mg/kg in 2 dogs. Elevated sedimention rate, slightly reduced lymphocytes with increase in segmented neutrophils and decrease in eosinophils.	Reduced adrenal, testes and prostate weight for all cyproterone acetate treated animals. Ovary and uterus weights reduced at 100 mg/kg. Liver weight slightly increased for some dogs. Histopathology: Marked adrenal atrophy of zona fasciculata and reticularis, testicular atrophy and absence of spermatogenesis, some Leydig cell hyperplasia, prostatic atrophy, ovarian and uterine atrophy, hyperplasia of mammary gland in males and females.
Rhesus Monkey 4/females/ dose	0, 0.04, 0.4 and 40 mg/kg 12 weeks oral	No mortality or behaviour changes. Dose related alopecia. Raised insulin level above 0.04 mg/kg. Negative influence on coagulation at 0.4 mg/kg and 40 mg/kg. Stimulation of ACTH cells at 0.4 mg and above. Increase in prolactin cells and slight reduction in gonadotrophin cells. Galactorrhea in all treated.	At doses of 0.4 mg/kg and above - diffuse liver cell hypertrophy and an increase in smooth endoplasmic reticulum. At the two highest doses, 2 and 3 animals also had occasional eosinophil cytoplasmic inclusion bodies in the liver cells. In most treated animals small mammary nodules were palpable in the glandular tissue; at 40 mg/kg slight ductus proliferation was also noted.

Fertility and Reproduction Study

Animal Species	Route of Administration and Dosage	Findings
Rats 24/sex/dose (2 generations)	0, 0.4, 4.0 and 40 mg/kg, oral	*0.4 mg/kg:* No influence by drug on fertility of the P1 and F1 generations. *4 mg/kg:* Significant decrease in body weights but no impairment of pre- and post-natal development. *40 mg/kg:* Food intake and body weight gain reduced. Although attempted matings were increased, less than 50% of the females had litters. No specific pathological changes were found in the dams, fetuses or young. Similarly, no malformations were observed.

Mutagenicity

No mutagenic effect of cyproterone acetate was demonstrated in either *in vitro* (*Salmonella typhimurium*) or *in vivo* (micronucleus test in the monkey).

CLINICAL SUMMARY

Clinical Studies

A total of 24 studies have been conducted with cyproterone acetate in patients requiring palliative treatment for advanced prostatic carcinoma. Worldwide, more than 1000 patients have participated in these studies, which included several large multicentre trials in addition to the important comparative multicentre trial conducted by the European Cancer Oncology group. North American experience has been accumulated in the U.S. by Drs. Scott (John Hopkins Hospital, Baltimore), Geller (Mercy Hospital and Medical Center, San Diego), and by Drs. Wein and Murphy (Hospital of the University of Pennsylvania, Philadelphia). There is now an ongoing study being conducted by Dr. Bruchovsky and the Cancer Oncology Group at the University of British Columbia.

Patients and Stage of Disease

As shown in Table I, more than 90% of the patients treated with cyproterone acetate had C-level advanced prostatic carcinoma, or D1 or D2 prostatic carcinoma with metastasis.

Table I - Patients

Stage	No. of Patients
A or B	18
C	174
C or D	502
D	349
Not specified	39
Total	1082

The majority of patients (75%) had no therapy prior to treatment with cyproterone acetate. A large group of patients had received various types of estrogen therapy, but had proven to be refractory or unable to tolerate the drug. A few patients had undergone an orchiectomy or had received radiation therapy (Table II).

Table II - Previous Therapy	
Therapy	**No. of Patients**
None	809
Orchiectomy	76
Estrogen	253
Radiation	16

Dosage and Administration

The oral route of administration of cyproterone acetate was employed in 910 patients (84%), while 172 patients received an oily solution containing 100 mg/mL cyproterone acetate. The standard dose of the latter was one weekly i.m. injection of 300 mg. As shown in the table below (Table III), the daily oral dose varied considerably from study to study and from patient to patient. However, most patients were treated with doses ranging from 200 - 300 mg/day. In orchiectomized patients, the daily dose was generally reduced by about 50% to a range of 100 - 200 mg/day orally or the frequency of cyproterone acetate depot injections was reduced to one every 2 weeks.

Table III - Dose of Cyproterone Acetate or Oily Solution Containing 100 mg/mL Cyproterone Acetate			
Entity	**Route**	**Dose**	**No. of Patients**
Cyproterone acetate	Oral	100 mg/day 200 mg/day 250 mg/day 300 mg/day 100-300 mg/day	15 197 135 114 449
Injectable Oily Solution Containing 100 mg/mL Cyproterone acetate	i.m.	300 mg/week	172

Only 32 patients (3%) received concomitant drug therapy with cyproterone acetate. No other patients received concomitant drugs, but 521 patients (48%) underwent an orchiectomy (Table IV).

Table IV - Concomitant Therapy	
Therapy	**No. of Patients**
None	529
Estrogen (DES 0.1 mg)	32
Orchiectomy	521

Results of Clinical Investigations

Table V - Effect on Serum Testosterone and Prostatic Acid Phosphatase (PAP)		
Parameter	**No. of Studies**	**Result**
Serum testosterone	7	70-90% reduction
Prostatic acid phosphatase	11	Normalization in 90% of responding patients

The effect of cyproterone acetate on serum testosterone was monitored in 7 studies. Serum testosterone was rapidly reduced following daily oral doses of 200 - 300 mg, with castrate levels being achieved within 1 - 4 weeks. The reduction is usually in the order of 70 - 90%; the greatest percent reduction occurred when cyproterone acetate was combined with estrogen.
Results of PAP evaluations consistently showed a normalization of values within a very short time in responding patients. Similarly, when there are signs of progressive metastasis, PAP values again deviate from normal levels.

Effect on Primary Tumour (Table VI): The effect of cyproterone acetate on the primary tumour was assessed in a total of 678 patients. Of these, 489 were previously untreated; the primary tumour was reduced in 318 of these (65%) and was stabilized in another 69 (14%). Thus, the overall positive response rate in this group was 79%.

A significant, though smaller, percentage (59%) of estrogen-refractory patients also exhibited a positive result.

Table VI - Effect on Primary Tumour				
Patient Group	No.	Response of Primary Tumour		Total with Positive Effect
		Reduced	Stabilized	
Previously untreated	489	318 (65%)	69 (14%)	387 (79%)
Estrogen-refractory	189	112 (59%)	---	112 (59%)

Effect on Metastasis (Table VII): As shown in Table VII, metastasis was reduced in 31% of 216 evaluable patients who had not previously been treated, but in only 13% of the evaluable estrogen-refractory patients. The progression of metastases appeared to be time-dependent. Despite reduced serum testosterone levels, metastases will progress over a period of several months to years, even in patients who were initially stabilized. The major cause of death during therapy with cyproterone acetate was the progression of metastases and not the primary tumours.

Table VII - Effect on Metastases				
Patient Group	No.	Response of Metastases		Total with Positive Effect
		Reduced	Stabilized	
Previously untreated	216	67 (31%)	82 (39%)	149 (70%)
Estrogen-refractory	71	10 (13%)	7 (10%)	17 (23%)

Effect on Pain (Table VIII): Table VIII illustrates the incidence of pain relief reported in each of 13 studies. Pain relief was noted in approximately 50 - 80% of patients receiving treatment with cyproterone acetate. The effect of cyproterone acetate on pain generally parallelled its effect on metastases. As long as metastases remained improved or stabilized, the analgesic requirement was also reduced. Renewed analgesic requirements were frequently indicative of metastatic progression.

Table VIII - Pain Relief	
Investigator	**Incidence of Pain Relief**
Dr. Bracci	172/216
Dr. Giuliani	12/16
Dr. Smith	12/25
Dr. Scott	8/10
Dr. Geller	8/10
Dr. Mauermayer	38/58
Dr. Wein	13/24
Dr. Tveter	2/6
Dr. Di Silverio	13/20
Dr. Ah-Lan	9/16
Dr. Pescatore	12/16
Dr. Hermabessiere	2/4
Dr. Bruchovsky	15/24
Total	316/425 = 74%

Subjective and Objective Response (Table IX): A general improvement in the subjective assessment of the quality of life was achieved in 70% of the 367 evaluable patients (Table IX).

The objective evaluations of remissions shown in Table IX were based on ECOG criteria. The best results were obtained when cyproterone acetate was used in combination with orchiectomy. One study revealed that more than 1/3 of the patients treated with cyproterone acetate achieved a complete or partial remission for 3 - 5 years. The Canadian study found that a complete or partial remission was still evident in 75% of the patients after one year of treatment.

Table IX - Subjective and Objective Responses			
Subjective Responses			
No. Evaluable Patients		**No. Improved***	
367		255 (70%)	
Objective Responses (ECOG Criteria)			
Treatment	**Patient Group**	**No. Patients**	**No. with Complete or Partial Remissions**
Cyproterone Acetate	Previously untreated	270	134 (50%)
Cyproterone Acetate	Estrogen-refractory	77	31 (44%)
Cyproterone Acetate/ Orchiectomy	Previously untreated and/ or Estrogen-refractory	274	154 (60%)

*Based on criteria of general improvement in quality of life (i.e. weight gain, pain relief, etc.)

Survival Rate (Table X):

Table X - Survival Rate					
				Survival	
Investigator	No. Patients	Stage	Duration of Treatment	Cyproterone Acetate	Estrogen
Mauermayer	58	C or D	2-5 yrs	38/58 (70%)	--
Wein	55	A (7) C (25) D (23)	4 yrs	39/55 (70%)	--
Bracci	216	C or D	5 yrs	138/216(64%)	--
Di Silverio	20	D	Up to 38 mths	3/20 (15%)	--
Giuliani	68	C	5 yrs	30/68 (44%)	31%
Giuliani	38	D	3 yrs	10/38 (27%)	10%
Jacobi	51	C or D	2 yrs	18/40 (45%)	--
Pavone	103	C or D	3.5-5 yrs	42/103 (41%)	41%
Bruchovsky	29	D	9-15 mths	23/29 (80%)	--

As shown in the table above, 5-year survival rates ranged from 41 - 64%. The 3-year rate for D patients was 27% and 1- to 2-year rates varied from a low of 15% up to a high of 80%. These survival rates generally represented an improvement over results previously obtained with estrogen therapy.

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