PRODUCT MONOGRAPH

MYLAN-CYPROTERONE

Cyproterone Acetate Tablets

50 mg

House standard

ANTIANDROGEN

Mylan Pharmaceuticals ULC
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Etobicoke, Ontario
M8Z 2S6

Date of revision: September 9, 2010

Submission Control No.: 139740

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Cyproterone Acetate Tablets, House
50 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet, 50 mg	Lactose, Corn/Maize starch.

INDICATIONS AND CLINICAL USE

MYLAN-CYPROTERONE (cyproterone acetate) is indicated for:

- the palliative treatment of patients with advanced prostatic carcinoma.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Liver disease and hepatic dysfunction.
- Renal insufficiency.
- Dubin Johnson syndrome, Rotor syndrome
- Previous or existing liver tumors (only if these are not due to metastases from carcinoma of the prostate)
- Wasting diseases (with the exception of inoperable carcinoma of the prostate)
- Severe chronic depression
- Existing thromboembolic processes

WARNINGS AND PRECAUTIONS

General

Concomitant Alcohol: Alcohol may reduce the antiandrogenic effect of MYLAN-CYPROTERONE 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 MYLAN-CYPROTERONE 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 become much less pronounced from the third month on. Marked lassitude and asthenia necessitate special care when driving or operating machinery.

Carcinogenesis and Mutagenesis

Cyproterone acetate showed a potential to initiate and/or promote liver tumor formation in rodents.
Very rare cases of benign and malignant liver tumors have been observed in patients receiving cyproterone acetate.

Meningioma: Cerebral meningiomas (single and multiple) have been reported in association with long-term use (several years) of cyproterone acetate. If a patient treated with MYLAN-CYPROTERONE is diagnosed with a meningioma, MYLAN-CYPROTERONE must be stopped.

Antiandrogen Withdrawal Syndrome: In some patients with metastatic prostate cancer, antiandrogens (steroidal or nonsteroidal) may promote, rather than inhibit, the growth of prostate cancer. A decrease in PSA and/or clinical improvement following the discontinuation of antiandrogens has been reported. It is recommended that patients prescribed an antiandrogen, who have PSA progression, should have the antiandrogen discontinued immediately and be monitored for 6 to 8 weeks for a withdrawal response prior to any decision to proceed with other prostate cancer therapy.

Gynecomastia: Benign nodules (hyperplasia) of the breast have been reported; these generally subside 1 to 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 tumor control.

Endocrine and Metabolism

Adrenocortical Function: Suppression of adrenocortical function tests have occurred in patients receiving cyproterone acetate and preclinical data also suggest a possible suppression due to the corticoid-like effect of cyproterone acetate.

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

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

Diabetes: MYLAN-CYPROTERONE may impair carbohydrate metabolism. Parameters of carbohydrate metabolism, fasting blood glucose and glucose tolerance tests, should be examined carefully in all patients and particularly in all diabetics before and regularly during therapy with MYLAN-CYPROTERONE.

Strict medical supervision is necessary if the patient suffers from diabetes, because the requirement for oral antidiabetics or insulin can change during MYLAN-CYPROTERONE treatment.

Metabolic Effects: Fluid retention, hypercalcemia and changes in plasma lipid profile may occur. Accordingly, MYLAN-CYPROTERONE should be used with caution in patients with cardiac disease.

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

Hematologic

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

Thromboembolism: Clinical investigations have shown that when cyproterone acetate is used alone it has a minor effect on blood clotting factors. However, when cyproterone acetate was combined with ethinyl estradiol, changes were found in increased coagulation capability.

The occurrence of thromboembolic events has been reported in patients using cyproterone acetate, although a causal relationship has not been

established. Patients with previous arterial or venous thrombotic / thromboembolic events (eg, deep venous thrombosis, pulmonary embolism, myocardial infarction) or with a history of cerebrovascular accidents or with advanced malignancies are at increased risk of further thromboembolic events.

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 disorder occur: thrombophlebitis, cerebrovascular complications, retinal thrombosis, or pulmonary embolism.

In patients with inoperable carcinoma of the prostate, presenting with a history of thromboembolic processes or suffering from sickle cell anemia or from severe diabetes with vascular changes, a careful risk:benefit evaluation must be carried out in each individual case before MYLAN-CYPROTERONE is prescribed.

Hepatic/Biliary/Pancreas

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 to 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 pretreatment, at regular intervals during 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, eg, metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

In very rare cases, benign and malignant liver tumors which may lead to life-threatening intra-abdominal hemorrhage have been observed after the use of cyproterone acetate. If severe upper abdominal complaints, liver enlargement, or signs of intra-abdominal hemorrhage occur, a liver tumor should be included in the differential-diagnostic considerations.

Psychiatric

Depression: Cyproterone acetate therapy has occasionally been associated with an increased incidence of depressive mood changes,

especially during the first 6 to 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.

Respiratory

Shortness of Breath: A sensation of shortness of breath was commonly reported in patients treated with 300 mg/day cyproterone acetate. Patients with pre-existing pulmonary dysfunction are most likely to be affected.

Sexual Function/Reproduction

Inhibition of Spermatogenesis: The sperm count and the volume of ejaculate are reduced at oral doses of 50 to 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 to 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.

Skin

MYLAN-CYPROTERONE therapy may cause a reduction of sebum production leading to dryness of the skin and transient patchy loss of body hair.

Special Populations

Pregnant Women
Treatment with MYLAN-CYPROTERONE is not indicated for use in women.

Nursing Women
Treatment with MYLAN-CYPROTERONE is not indicated for use in women.

Pediatrics
MYLAN-CYPROTERONE is not recommended for use in children and adolescents below 18 years of age.
MYLAN-CYPROTERONE must not be given before the conclusion of puberty since an unfavorable influence on longitudinal growth and the still unstabilized axes of endocrine function cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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: decreased libido, breast enlargement, breast tenderness, benign nodular hyperplasia of the breast, galactorrhea, gynecomastia, abnormal spermatozoa, impotence, and inhibition of spermatogenesis.

The most serious adverse drug reactions (ADRs) in patients receiving cyproterone acetate are hepatic toxicity, benign and malignant liver tumors which may lead to intra-abdominal hemorrhage, and thromboembolic events.

As with other antiandrogenic treatments, long-term androgen deprivation with cyproterone aceate may lead to osteoporosis.

Other adverse events which have been reported are listed below:

Cardiovascular System: hypotension, tachycardia, heart failure, syncope, myocardial infarct, hemorrhage, cerebrovascular accident, cardiovascular 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, cholestatic jaundice, cirrhosis of liver, hepatic coma, hepatitis, hepatoma, hepatomegaly, jaundice, liver carcinoma (for further information see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreas**), liver failure (for further information see **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreas**),

abnormal liver function test, liver necrosis, pancreatitis, glossitis.

Hematology: increased fibrinogen, decreased prothrombin, thrombocytopenia, anemia (for further information see **WARNINGS AND PRECAUTIONS – Hematologic**), 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.

Central Nervous System: fatigue, lassitude, weakness, hot flashes, increased sweating, aphasia, coma, depression, dizziness, encephalopathy, hemiplegia, personality disorder, psychotic depression, abnormal gait, headache, temporary restlessness.

Cerebral meningiomas (single and multiple) have been reported in association with long-term use (several years) of cyproterone acetate (see **WARNINGS AND PRECAUTIONS - Carcinogenesis and Mutagenesis).**

Respiratory System: asthma, increased cough, dyspnea, hyperventilation, respiratory disorder, shortness of breath on effort (see **WARNINGS AND PRECAUTIONS - Respiratory**), lung fibrosis.

Skin: eczema, urticaria, erythema nodosum, exfoliative dermatitis, rash, maculopapular rash, dryness of the skin, pruritus, alopecia, hirsutism, skin discoloration, 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.

DRUG INTERACTIONS

Overview

Although clinical interaction studies have not been performed, since this drug is metabolized by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir, and other strong inhibitors of CYP3A4 inhibit the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as rifampicin, phenytoin, and products containing St. John´s wort may reduce the levels of cyproterone acetate.

Based on in vitro inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4, and 2D6 is possible at high therapeutic cyproterone acetate doses of 300 mg daily. In addition, cyproterone acetate was also shown to increase the enzymatic activity of CYP1A2 and CYP2E1 in vitro. Caution should be exercised when MYLAN-CYPROTERONE is to be co-administered with a substrate of the P450 enzymes.

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMGCoA inhibitors (statins) which are primarily metabolized by CYP 3A4 are coadministered with high therapeutic cyproterone acetate doses, since they share the same metabolic pathway.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with Hepatic Impairment

The use of MYLAN-CYPROTERONE is contraindicated in patients with liver diseases and/or with hepatic dysfunction.

Patients with Renal Impairment

A pharmacokinetic study in patients with renal impairment has not been

conducted. As 33% of cyproterone acetate is excreted via the kidney, caution should be taken when MYLAN-CYPROTERONE is administered in this patient population.

Recommended Dose and Dosage Adjustment

The usual daily initial and maintenance dose of MYLAN-CYPROTERONE (cyproterone acetate) is 4 to6 tablets (200-300 mg) divided into 2 to3 doses and taken with some liquid after meals.

The maximum daily dose is 300 mg.

MYLAN-CYPROTERONE therapy should not be interrupted nor the dosage reduced after remission or improvement occurs.

The dosage may be reduced if side effects are intolerable but should be kept within the range of 2 to 6 tablets (100-300 mg) at weekly intervals, or every 2 weeks.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 feed-back on the hypothalamo-pituitary axis, by inhibiting the secretion of LH leading to diminished production of testicular testosterone.

Pharmacokinetics

Absorption

The absorption of cyproterone acetate following oral administration is complete. Peak plasma levels are reached 3 to 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.

Metabolism

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

Excretion

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.

STORAGE AND STABILITY

Store at room temperature between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYLAN-CYPROTERONE comes in tablets containing 50 milligrams (mg) of cyproterone acetate as the active ingredient. MYLAN-CYPROTERONE is available as white to off-white, round, flat, bevel edged tablets marked with “CY” breakline “50” on one side and “G” on the other side of 60 tablets.

The non-medicinal ingredients include: Colloidal Silicon Dioxide, Corn/Maize Starch, Lactose, Magnesium Stearate, and Povidone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

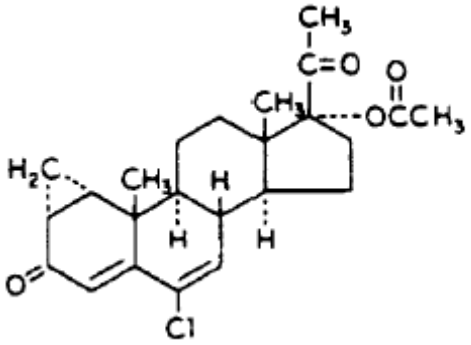
Proper Name: Cyproterone Acetate

Chemical Name: 6-chloro-17α-hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione-acetate

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

Molecular weight: 416.95

Structural formula:



Physicochemical properties: Cyproterone acetate is a white or slightly yellowish crystalline powder.

Solubilities: Totally soluble in chloroform; very soluble in acetone and benzene; soluble in ethanol and methanol, slightly soluble in petroleum ether. Practically insoluble in water. The solubility in buffered aqueous system has been determined to be approximately 10 g/L.

Melting Point: Between 210° C to 214° C

COMPARATIVE BIOAVAILABILITY

Bioavailability Study

A comparative bioavailability study was performed between MYLAN-CYPROTERONE (cyproterone acetate) 50 mg TABLETS and the 50 mg strength of the Canadian reference product. Twenty-nine healthy male volunteers completed the study. The pharmacokinetic data for both formulations is tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Cyproterone Acetate

(2 x 50 mg Tablets)

From measured and log transformed data

	GEOMETRIC MEAN ARITHMETIC MEAN (CV%)			
	Mylan-Cyproterone	*Androcur®**	% RATIO OF GEOMETRIC MEANS	90% CONFIDANCE INTERVAL
$AUC_{(O-T)}$ (ng.hr/mL)	6229.8 6724.5 (34.7)	6821.0 7082.2 (28.9)	94.9 ----	80.3-103.0 ----
$AUC_{(O-72)}$ (ng.hr/mL)	4244.0 4436.7 (26.1)	4476.5 4577.9 (22.8)	96.9 ----	84.5-105.5 ----
$AUC_{(O-inf)}$ (ng.hr/mL)	6907.9 7398.0 (35.0)	7449.2 7758.2 (30.5)	95.4 ----	83.1-102.7 ----
C_{MAX} (ng/mL)	242.0 267.3 (45.6)	251.8 266.9 (37.9)	100.2 ----	81.0-113.1 ----
T_{MAX} (hr)	--- 2.34 (32.8)	--- 2.69 (76.3)	---- ----	---- ----
$T_{1/2}$ (hr)	--- 74.5 (26.9)	---- 74.2 (34.2)	---- ----	---- ----

T_{MAX} and $T_{1/2}$ parameters are expressed as the arithmetic means (CV%) only.

*Androcur® Tablets 50 mg, Berlex Canada, were purchased in Canada.

CLINICAL TRIALS

A total of 24 studies have been conducted with cyproterone acetate in patients requiring palliative treatment for advanced prostatic carcinoma. Worldwide, more than 1,000 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 (Johns Hopkins Hospital, Baltimore), Geller (Mercy Hospital & Medical Center, San Diego), and by Drs. Wein and Murphy (Hospital of the University of Pennsylvania, Philadelphia).

Study Demographics and Trial Design

Patients and Stage of Disease

As shown in Table 2, more than 90% of the patients treated with cyproterone acetate had stage C advanced prostatic carcinoma, or stage D1 or D2 prostatic carcinoma with metastasis.

Table 2: 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 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 3).

Table 3: Previous Therapy

Previous 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%). As shown in the table below (Table 4), 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 to 300 mg/day. In orchiectomized patients, the daily dose was generally reduced by about 50% to a range of 100 to 200 mg/day orally.

Table 4: Dose of cyproterone acetate

Entity	Route	Dose	No. of Patients
Cyproterone acetate	Oral	100 mg/day	15
		200 mg/day	197
		250 mg/day	135
		300 mg/day	114
		100-300 mg/day	449

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 5).

Table 5: Concomitant Therapy

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

Study Results

Effect on Serum Testosterone and Prostatic Acid Phosphatase (PAP)

Table 6: 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 (Table 6). Serum testosterone was rapidly reduced following daily oral doses of 200 to 300 mg, with castrate levels being achieved within 1 to 4 weeks. The reduction was usually in the order of 70% to 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 were signs of progressing metastasis, PAP values again deviated from normal levels.

Effect on Primary Tumor

The effect of cyproterone acetate on the primary tumor was assessed in a total of 678 patients. Of these, 489 were previously untreated; the primary tumor 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% (Table 7).

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

Table 7: Effect on Primary Tumor

Patient Group	Number	Response of Primary Tumor		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

As shown in Table 8, 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 progressed 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 tumors.

Table 8: Effect on Metastases

Patient Group	Number	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 9 illustrates the incidence of pain relief reported in each of 13 studies. Pain relief was noted in approximately 50 to 80% of patients receiving treatment with cyproterone acetate. The effect of cyproterone acetate on pain generally paralleled 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 9: 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 Responses

A general improvement in the subjective assessment of the quality of life was achieved in 70% of the 367 evaluable patients (Table 10).

The objective evaluations of remissions shown in Table 10 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 10: Subjective and Objective Responses

Subjective Responses			
No. Evaluable Patients		**No. Improved[a]**	
367		255 (70%)	
Objective Responses (ECOG Criteria)			
Treatment	**Patient Group**	**No. of 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%)

a Based on criteria of general improvement in quality of life (ie, weight gain, pain relief, etc.)

Survival Rate

Table 11: Survival Rate

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

As shown in Table 11 above, 5-year survival rates ranged from 41% to 64%. The 3-year rate for stage 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.

DETAILED 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.

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 1to 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 hydrolysed, and mainly cyproterone acetate and the metabolite 15β-hydroxycyproterone 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 to 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, biotransformation, and metabolic spectra of cyproterone acetate are similar in man and the rhesus monkey.

Human 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.

Progestenic and Antigonadothrophic 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.

Pharmacokinetics

A bioavailability study was performed in 5 male volunteer subjects receiving a single oral dose of 50 mg 14C-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/L (=290µg /L) cyproterone acetate or, including the radioactivity of metabolites, 960 nmol/L (=400µg /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).

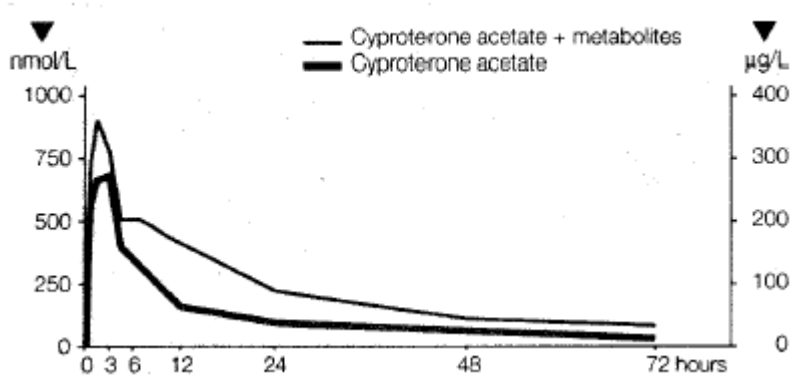


Figure 1: Relationship of Unchanged Cyproterone Acetate to the Total 14C-labelled Substance (Cyproterone Acetate + Metabolites) in the Plasma of a Male Subject Following Oral Administration of 50 mg 14Ccyproterone Acetate

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).

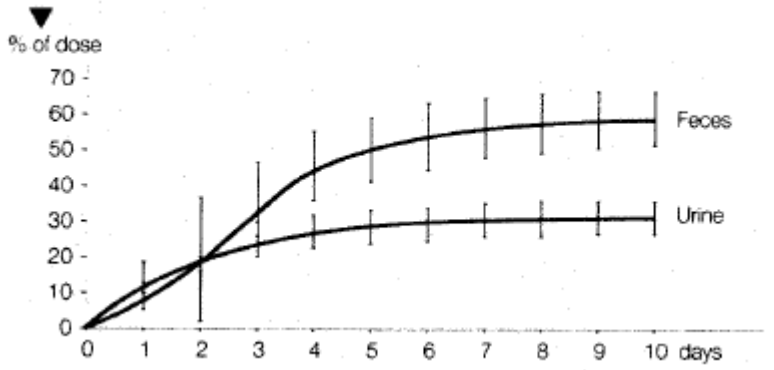


Figure 2: Elimination (% of Dose) Following Oral Administration of 50 mg 14C-cyproterone Acetate in Male Subjects. Mean Values ± Standard Deviation (n=5)

TOXICOLOGY

Cyproterone acetate has been found at low doses of 2 to 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 to 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 preneoplastic, 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 tumors in man.

Acute Toxicity

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

Table 12: LD_{50} After Single Application of Cyproterone Acetate

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 nontoxic following single dose administration. The maximum intramuscular doses were also tolerated without symptoms in the dog, with exception of local tolerance manifestation.

Repeated Dose Toxicity

Chronic Toxicity Studies

Table 13: Chronic Toxicity Studies

Animal Species	Dosage (mg/kg) 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 increase: 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), discolored kidneys with rough surfaces.
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 discoloration and nodules; atrophy of testes, seminal vesicles, and prostate. Increased incidence of mammary neoplasms (adenomas and adenocarcinomas).

Animal Species	Dosage (mg/kg) and Duration	Mortality and Clinical and Laboratory Observations	Necropsy and Histopathology
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.

Reproductive Toxicology

Table 14: Fertility and Reproduction Study

Animal Species	Route and Dosage of Administration	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.

Mutagenesis

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

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PART III: CONSUMER INFORMATION

MYLAN-CYPROTERONE
cyproterone acetate tablets, House

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-CYPROTERONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN- CYPROTERONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MYLAN-CYPROTERONE is indicated for the palliative treatment of patients with advanced prostate cancer.

What it does:
MYLAN-CYPROTERONE is a drug acting against male sex hormones (androgens). Androgens encourage the growth of prostate cancer and MYLAN-CYPROTERONE inhibits this effect.

When it should not be used:

Do not take MYLAN-CYPROTERONE if you:

- are allergic (hypersensitive) to cyproterone acetate or any of the other ingredients of MYLAN-CYPROTERONE;
- have a liver disease or reduced liver function;
- have Dubin-Johnson syndrome or Rotor syndrome that affects the excretion of red blood cell pigment (bilirubin);
- have or have had liver tumors that are not due to the spread of prostate cancer;
- have reduced kidney function;
- have wasting diseases that are not related to prostate cancer;
- suffer from severe chronic depression;
- have conditions that increase your risk for developing blood clots (thromboembolic process).

What the medicinal ingredient is:
MYLAN-CYPROTERONE comes in tablets containing 50 milligrams (mg) of cyproterone acetate as the active ingredient.

What the nonmedicinal ingredients are:
Each tablet contains the following inactive ingredients: Colloidal Silicon Dioxide, Corn/Maize Starch, Lactose, Magnesium Stearate, and Povidone.

What dosage forms it comes in:
MYLAN-CYPROTERONE comes in bottles of 60 tablets.

WARNINGS AND PRECAUTIONS

MYLAN-CYPROTERONE may decrease the function of the hormoneproducing glands attached to the kidney (adrenal glands). Therefore your doctor may conduct some tests to monitor this effect during treatment with MYLAN-CYPROTERONE .

BEFORE you use MYLAN-CYPROTERONE talk to your doctor or pharmacist if you have or have had any of the following conditions:

- Blood clots;
- Liver problem;
- Depression;
- Breathing problem (shortness of breath).
- Diabetes. Your doctor may need to adjust your antidiabetic medication. This requires strict supervision during treatment with MYLAN-CYPROTERONE.
- Anemia. Your doctor will monitor your red-blood cell count during treatment.

MYLAN-CYPROTERONE is not recommended for use in children and adolescents below 18 years of age and before the end of puberty, as it may have a negative effect on growth and the immature hormonal regulation functions.

MYLAN-CYPROTERONE is not recommended for use in women.

INTERACTIONS WITH THIS MEDICATION

- Drugs that may interact with MYLAN-CYPROTERONE include:
- Statins (medicines for reducing blood fats)
- Ketoconazole, itraconazole, clotrimazole (for fungal infections)
- Ritonavir (for viral infections)
- Rifampicin (for tuberculosis)
- Phenytoin (for epilepsy)
- St. John's Wort (herbal remedy for depression)

PROPER USE OF THIS MEDICATION

You should follow the dose prescribed by your doctor.

Usual dose
200 mg to 300 mg daily taken orally in two or three divided doses with liquid after meals. Maximum daily dose is 300 mg.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Do not take the missed MYLAN-CYPROTERONE (do not take a double dose to make up for the missed tablet). Continue taking the tablets at the regular time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MYLAN-CYPROTERONE can have side effects, like all medicines, but not everybody gets them. For further information about any of these effects, ask a doctor or pharmacist.

If any of the side effects get serious, or if you notice any side effects not listed here, please tell your doctor or pharmacist.

Very frequent side effects:
- Reduced sexual interest (decreased libido)
- Swelling of the breast, breast soreness (gynecomastia)
- Impotence
- Abnormal sperm, low sperm count which may be reversible after MYLAN-CYPROTERONE is discontinued.

Other side effects:
- Hair loss or unusual increase in hair growth
- Constipation or diarrhea (loose stools)
- Weight gain
- Tiredness and weakness
- Shortness of breath
- Skin rash, blisters
- Vision change
- Decrease in blood pressure
- Increase in blood sugar
- Depression

Rare but serious side effects:

- Liver toxicity: generally feeling unwell, fever, nausea, vomiting, loss of appetite, itching, yellowing of the skin and eyes, light-colored stools, dark-colored urine
- Life-threatening internal bleeding (intra-abdominal hemorrhage): unusual upper abdominal pains which do not disappear within a short time
- Blood clots: swelling of the calf or leg (blood clots in the leg), chest pain and being short of breath (blood clots in the lung), suddenly feeling weak, loss of coordination, slurred speech (a stroke or blood clots in the brain), temporary blindness (blood clots in the eye)

Bone loss (osteoporosis) and benign brain tumors (cerebral meningioma) have been reported with long term use of MYLAN-CYPROTERONE

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Inability to achieve or maintain an erection	√		
Liver toxicity, (generally feeling unwell, fever, nausea, vomiting, loss of appetite, itching all over the body, yellowing of the skin or eyes, light colored bowel movements, dark urine) liver inflammation (hepatitis), liver failure			√
Reduced sexual drive	√		
Reversible inhibition of sperm production	√		
Swelling of the calf or leg, chest pain, suddenly feeling weak			√
Unusual upper abdominal pains which do not disappear within a short time			√

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-CYPROTERONE , contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.
Do not take MYLAN_CYPROTERONE after the expiry date which is stated on the pack.

Medicines must not be disposed of via wastewater or household waste. Ask you pharmacist how to dispose of medicine no longer required. These measures will help to protect the environment.

Store at room temperature between 15°C and 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  -Fax toll-free to 1-866-678-6789, or
  -Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information leaflet plus the full Monograph, prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379 or at customerservice@mylan.ca.

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Last revised: September 9, 2010