PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrANDROCUR®

cyproterone acetate tablets

50 mg

PrANDROCUR® DEPOT

Cyproterone acetate injection

100 mg/mL

Antiandrogen

Bayer Inc.
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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

ANDROCUR (cyproterone acetate) is indicated for:

- the palliative treatment of patients with advanced prostatic carcinoma

2. 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 6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- Liver disease and hepatic dysfunction
- Dubin Johnson syndrome, Rotor syndrome
- Previous or existing liver tumors (only if these are not due to metastases from carcinoma of the prostate)
- Presence or history of meningioma
- Wasting diseases (with the exception of inoperable carcinoma of the prostate)
- Severe chronic depression
- Existing thromboembolic processes

3. SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ANDROCUR and ANDROCUR DEPOT should be prescribed and managed by a qualified physician experienced in the use of hormonal therapy in prostate cancer. The following are clinically significant adverse events:

- Hepatotoxicity with acute hepatic failure (see Hepatic/Biliary/Pancreatic, Hepatotoxicity).

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients with Hepatic Impairment

The use of ANDROCUR 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 ANDROCUR is administered in this patient population.

4.2 Recommended Dose and Dosage Adjustment

Oral Tablets: The usual daily initial and maintenance dose of ANDROCUR (cyproterone acetate) is 4 to 6 tablets (200-300 mg) divided into 2 to 3 doses and taken with some liquid after meals.

The maximum daily dose is 300 mg.

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

Injectable: The usual initial and maintenance dose of ANDROCUR DEPOT is one weekly intramuscular injection of 3 mL (300 mg). For orchiectomized patients, the recommended dose is one intramuscular injection of 3 mL (300 mg) every two weeks.

ANDROCUR or ANDROCUR DEPOT therapy should not be interrupted nor the dosage reduced after remission or improvement occurs.

Because of their pharmacokinetic properties, ANDROCUR (oral) and ANDROCUR DEPOT (IM) can be interchanged in the course of long-term treatment. The dosage may be reduced if side effects are intolerable, but should be kept within the oral range of 2 to 6 tablets daily (100-300 mg) or intramuscular injections of 300 mg at weekly intervals, or every two weeks.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

This information is not available.

4.4 Administration

ANDROCUR DEPOT is strictly for intramuscular injection. The injections must be administered very slowly. Special care must be given to avoid intravascular injection (see 7. WARNINGS AND PRECAUTIONS).

5. OVERDOSAGE

There have been no reports of fatal overdosage in man with ANDROCUR (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.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1- Dosage forms, Strengths, Compositions and Packaging.

Route of Administration	Dosage Form/ Strength/ Composition	Non-medicinal ingredients
Oral	Tablet, 50 mg	Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, and povidone 25
Intramuscular	Intramuscular solution, 100 mg/mL	benzyl benzoate in a castor oil solution

ANDROCUR (cyproterone acetate) 50 mg tablet is presented as white to faintly yellowish, round, flat-sided tablet with bevelled edges, imprinted on one side with “BV” in a regular hexagon, the other side is scored.

ANDROCUR DEPOT 3 mL (300 mg) ampoules.

7. WARNINGS AND PRECAUTIONS

Please see the 3. SERIOUS WARNINGS AND PRECAUTIONS Box at the beginning of PART I: HEALTH PROFESSIONAL INFORMATION.

General

Concomitant Alcohol: Alcohol may reduce the antiandrogenic effect of ANDROCUR 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 ANDROCUR 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.

Other Conditions: As with all oily solutions, ANDROCUR DEPOT must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can in some cases lead to signs and symptoms such as cough, dyspnea, and chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, haemorrhages, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, eg, by administration of oxygen.

Concomitant Use With a GnRH Agonist or Orchiectomy: Based on a retrospective meta-analysis, long-term combination therapy of ANDROCUR with either orchiectomy or a GnRH agonist as treatment of patients with advanced prostate cancer may result in a 5-year survival disadvantage compared to castration alone.

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 ANDROCUR.

Meningioma: The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate. In a retrospective cohort study using data from a primary care database, meningiomas were reported very rarely in patients treated with cyproterone acetate for prostate cancer after several months of treatment; in these cases, causality was not established. If a patient treated with ANDROCUR is diagnosed with a meningioma, treatment with cyproterone containing products, including ANDROCUR must be permanently stopped. Patients with prehistory or presence of meningioma should not be treated with ANDROCUR (see 2. CONTRAINDICATIONS).

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 ANDROCUR and preclinical data also revealed a suppression of adrenal gland due to the administration of cyproterone acetate (see 16. NON-CLINICAL TOXICOLOGY).

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: ANDROCUR 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 ANDROCUR.

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

Metabolic Effects: Fluid retention, hypercalcemia and changes in plasma lipid profile may occur. Accordingly, ANDROCUR 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 ANDROCUR. Regular hematological assessment is recommended.

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

The occurrence of thromboembolic events has been reported in patients using ANDROCUR, 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.

ANDROCUR 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 ANDROCUR is prescribed.

Hepatic/Biliary/Pancreatic

Hepatotoxicity: Direct hepatic toxicity, including jaundice, hepatitis, and acute hepatic failure has been observed in patients treated with ANDROCUR. At daily doses of 100 mg and above, cases with fatal outcome have also been reported. Most reported fatal cases were in men treated with cyproterone acetate for prostatic cancer. Hepatotoxicity is dose-related and develops, usually, a few weeks to several months after cyproterone 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, ANDROCUR should be withdrawn. Benefit and risk should be evaluated carefully if any drug(s) with known hepatotoxicity is to be used concurrently with ANDROCUR. ANDROCUR should not be used in patients with prior history or existing hepatic disease (see 2. CONTRAINDICATIONS).

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

Monitoring and Laboratory Tests

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.

With the potential for adrenal gland suppression, it is recommended that adrenocortical function tests should be monitored periodically by serum cortisol assay.

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 ANDROCUR.

During treatment with ANDROCUR, serum electrolytes and complete blood counts should be performed regularly. Liver function tests should be performed pretreatment, at regular intervals during treatment, and whenever any symptoms or signs suggestive of hepatotoxicity occur.

Psychiatric

Depression: ANDROCUR 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 ANDROCUR. Patients with pre-existing pulmonary dysfunction are most likely to be affected.

Reproductive Health

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 ANDROCUR, or in some patients, after up to 20 months. Production of abnormal spermatozoa during ANDROCUR therapy has been observed; their relationship to abnormal fertilization or malformed embryos is not known.

Skin

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

7.1 Special Populations

7.1.1 Pregnant Women

Treatment with ANDROCUR is not indicated for use in women.

7.1.2 Breast-feeding

Treatment with ANDROCUR is not indicated for use in women.

7.1.3 Pediatrics

ANDROCUR is not recommended for use in children and adolescents below 18 years of age.

ANDROCUR 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.

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse events associated most frequently with the use of ANDROCUR 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 ANDROCUR 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 ANDROCUR 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, pulmonary oil microembolism, vasovagal reactions.

Gastrointestinal System: constipation, diarrhea, indigestion, anorexia, nausea, vomiting, cholestatic jaundice, cirrhosis of liver, hepatic coma, hepatitis, hepatoma, hepatomegaly, jaundice, liver carcinoma,

liver failure (for further information see 7. WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic), abnormal liver function test, liver necrosis, pancreatitis, glossitis.

Hematology: increased fibrinogen, decreased prothrombin, thrombocytopenia, anemia (for further information see 7. 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.

Meningiomas (single and multiple) have been reported in association with long-term use (several years) of ANDROCUR. In a retrospective cohort study using data from a primary care database, meningiomas were reported very rarely in patients treated with cyproterone acetate for prostate cancer after several months of treatment; in these cases, causality was not established (see 7. WARNINGS AND PRECAUTIONS - Carcinogenesis and Mutagenesis).

Respiratory System: asthma, increased cough, dyspnea, hyperventilation, respiratory disorder, shortness of breath on effort (see 7. 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.

8.2 Clinical Trial Adverse Reactions

The clinical trial data on which the original indication was authorized is not available.

8.3 Less Common Clinical Trial Adverse Reactions

The clinical trial data on which the original indication was authorized is not available.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The clinical trial data on which the original indication was authorized is not available.

8.5 Post-Market Adverse Reactions

Meningioma.

9. DRUG INTERACTIONS

9.2 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 ANDROCUR 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.

9.3 Drug-Behavioural Interactions

This information is not available for this drug product.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ANDROCUR (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.

10.3 Pharmacokinetics

Absorption:

ANDROCUR

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.

ANDROCUR DEPOT

Following intramuscular administration, mean maximum blood levels are attained 3.4 days after injection. The mean elimination half-life was found to be 4 days.

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.

Detailed 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.

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.

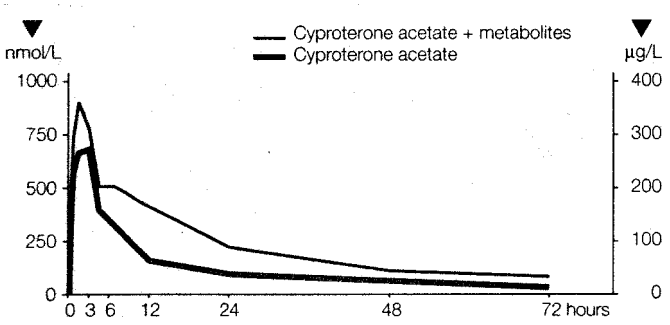
Pharmacokinetics

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/L (=290µg/L) cyproterone acetate or, including the radioactivity of metabolites, 960 nmol/L (=400µg /L) cyproterone acetate equivalent.

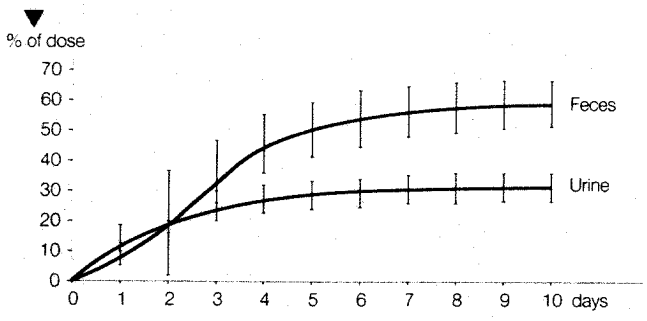
The plasma levels fell quickly up to 24 hours after administration because of extensive tissue distribution. The half-life of cyproterone acetate in plasma was calculated as 38 ± 5 hours (see Figure 1).

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

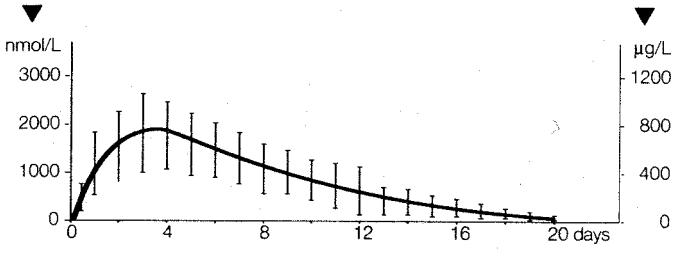
Figure 2: Elimination (% of Dose) Following Oral Administration of 50 mg ^{14}C-cyproterone Acetate in Male Subjects. Mean Values ± Standard Deviation (n=5)



The intramuscular injection of 300 mg radioactivity labelled cyproterone acetate in a castor oil solution corresponding to ANDROCUR DEPOT was administered to male patients.

The maximum plasma level was reached 82 ± 21 hours after administration. Half the maximum value could be seen less than 24 hours after administration; the values did not fall below this level until about 10 days after dosing (see Figure 3).

Figure 3: Plasma Levels (Cyproterone Acetate Equivalents/mL) Following IM injection of 300 mg Cyproterone Acetate in Oily Solution in Male Patients. Mean Values ± Standard Deviation (n=11)



The elimination half-life of the cyproterone acetate released from the depot was 38 ± 14 hours which is the same as measured under oral administration.

A steady-state study was also carried out in 5 patients who received 300 mg of ANDROCUR DEPOT on a weekly basis. Determinations of the cyproterone acetate concentrations were carried out after the first, third, and fifth injections. Table 2 summarizes the results of the study.

In man, cyproterone acetate is eliminated in the urine mainly in the form of unconjugated metabolites and in the bile in the form of glucuronized metabolites; the main metabolite was 15β-OH cyproterone acetate.

Table 2: Pharmacokinetic Parameters After One and Several Intramuscular Injections of 300 mg Cyproterone Acetate in an Oil Solution (ANDROCUR DEPOT) in 5 Patients (Mean Values ± SD).

Parameter	1st Injection	3rd Injection	5th Injection
t_{max} (d)	1.8 ± 0.4	2.4 ± 0.5	3.0 ± 1.0
C_{max} (ng/mL)	273 ± 54	387 ± 111	406 ± 57
$t_{½}$ (d)	4.4 ± 1.9	4.1 ± 1.3	3.9 ± 1.3

11. STORAGE, STABILITY AND DISPOSAL

This information is not available for this drug product

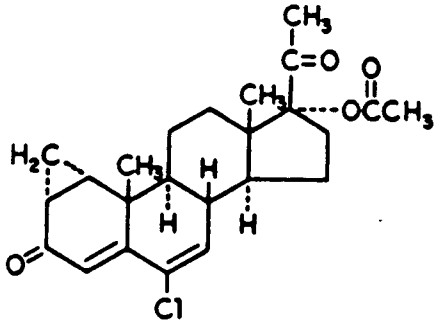
12. SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

13. 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 and molecular mass:	$C_{24}H_{29}ClO_4$, 416.95
Structural formula:	
Physicochemical properties:	White to faintly yellow micronized powder. Insoluble in water, very freely soluble in chloroform and dioxane. Melting range is 206-213ºC.

14. CLINICAL TRIALS

A total of 24 studies have been conducted with ANDROCUR (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).

14.1 Trial Design and Study Demographics

Patients and Stage of Disease

As shown in Table 3, more than 90% of the patients treated with ANDROCUR had stage C advanced prostatic carcinoma, or stage D1 or D2 prostatic carcinoma with metastasis.

Table 3: 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 ANDROCUR. 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 4).

Table 4: Previous Therapy

Previous Therapy	No. of Patients
None	809
Orchiectomy	76
Estrogen	253
Radiation	16

Dosage and Administration

The oral route of administration of ANDROCUR was employed in 910 patients (84%), while 172 patients received ANDROCUR DEPOT, an oily solution containing 100 mg/mL cyproterone acetate. The standard dose of the latter was one weekly IM injection of 300 mg. As shown in the table below (Table 5), 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 or the frequency of ANDROCUR DEPOT injections was reduced to one every 2 weeks.

Table 5 Dose of ANDROCUR or ANDROCUR DEPOT

Entity	Route	Dose	No. of Patients
ANDROCUR	Oral	100 mg/day	15
		200 mg/day	197
		250 mg/day	135
		300 mg/day	114
		100-300 mg/day	449
ANDROCUR DEPOT	IM	300 mg/week	172

Only 32 patients (3%) received concomitant drug therapy with ANDROCUR. No other patients received concomitant drugs, but 521 patients (48%) underwent an orchiectomy (Table 6).

Table 6: Concomitant Therapy

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

14.2 Study Results

Effect on Serum Testosterone and Prostatic Acid Phosphatase (PAP)

Table 7: 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 ANDROCUR on serum testosterone was monitored in 7 studies (Table 7). 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 ANDROCUR 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 ANDROCUR 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 8).

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

Table 8: 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 9, 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 ANDROCUR was the progression of metastases and not the primary tumors.

Table 9: 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 10 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 ANDROCUR. The effect of ANDROCUR 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 10: 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 11).

The objective evaluations of remissions shown in Table 11 were based on ECOG criteria. The best results were obtained when ANDROCUR was used in combination with orchiectomy. One study revealed that more than 1/3 of the patients treated with ANDROCUR achieved a complete or partial remission for 3 to 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 11: 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**
ANDROCUR	Previously untreated	270	134 (50%)
ANDROCUR	Estrogen-refractory	77	31 (44%)
ANDROCUR/ 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 12: Survival Rate

Investigator	No. of Patients	Stage	Duration of Treatment	Survival	
				ANDROCUR	Estrogen
Dr. Mauermayer	58	C or D	2 - 5 years	38/58 (70%)	-
Dr. Wein	55	A (7)	4 years	39/55 (70%)	-
		C (25)			
		D (23)			
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 12 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.

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

General Toxicology

ANDROCUR (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.

In repeat-dose studies conducted in rats (12 weeks) and dogs (54 weeks) with oral administration of cyproterone acetate, decreased adrenal weights in rats at 4.0 mg/kg/day and dogs at 10 mg/kg were noted. Marked atrophy of zona fasciculate and of zona reticularis with preservation of zona glomerulosa was also observed in the adrenal glands of all treated dogs.

Acute Toxicity

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

Table 13: LD_{50} After Single Application of Cyroterone 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

Repeat-dose toxicity studies revealed pathological changes in the liver, reproductive organs, adrenal glands, abnormal laboratory tests, and neoplasms of various tissues and organs in the animal species tested.

Chronic Toxicity Studies

Table 14: 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 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.

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 discoloration 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.

Mutagenesis and Carcinogenesis

Recognized first-line tests of genotoxicity gave negative results when conducted with CPA. No mutagenic effect of cyproterone acetate was demonstrated in either *in vitro* (Salmonella typhimurium) or *in vivo* (micronucleus test in the monkey). However, further tests showed that CPA was capable of producing DNA adducts 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 systemic 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**.** An initiating potential besides promoting effect of cyproterone acetate on the formation of ATPase deficient and γGT positive foci in female rat livers was noted. CPA also enhanced the frequencies of mutations in the livers of female transgenic rats in a dose-dependent manner, indicating that CPA is mutagenic.

Investigations into the tumorigenicity of cyproterone acetate did not reveal a specific tumorigenic potential in the liver of rodents although other neoplasms, including mammary adenocarcinoma in rats, were observed (see Table 14).

Reproductive Toxicology

Testicular atrophy and absence of spermatogenesis, some Leydig cell hyperplasia, prostatic atrophy, ovarian and uterine atrophy were observed in beagle dogs. A reduced number of pregnancies in untreated female rats was observed when male rats were administered with 40 mg/kg/day cyproterone acetate. The temporary inhibition of fertility in male rats brought about by daily oral treatment of cyproterone acetate did not result in malformations or impairment of fertility in the offspring produced by untreated female animals.

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.

Table 15: 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 postnatal 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.

Detailed 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 1 to 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr**ANDROCUR®**

cyproterone acetate tablets

Pr**ANDROCUR® DEPOT**

cyproterone acetate injection

Read this carefully before you start taking **ANDROCUR** and **ANDROCUR DEPOT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ANDROCUR** and **ANDROCUR DEPOT**.

Serious Warnings and Precautions

ANDROCUR and ANDROCUR DEPOT should be prescribed and managed by a doctor experienced with the treatment of prostate cancer. Treatment with ANDROCUR and ANDROCUR DEPOT may cause:

- Liver damage and liver failure
-

What is ANDROCUR and ANDROCUR DEPOT used for?

ANDROCUR and ANDROCUR DEPOT is used to reduce pain in the treatment of patients with advanced prostate cancer.

How does ANDROCUR and ANDROCUR DEPOT work?

ANDROCUR and ANDROCUR DEPOT contain the medicinal ingredient cyproterone acetate. It is an anti-androgen therapy. It blocks the actions of male sex hormones (androgens). Androgens promote the growth of prostate cancer.

What are the ingredients in ANDROCUR?

Medicinal ingredients: Cyproterone acetate.

Non-medicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch and povidone 25.

What are the ingredients in ANDROCUR DEPOT?

Medicinal ingredients: Cyproterone acetate.
Non-medicinal ingredients: benzyl benzoate in castor oil solution.

ANDROCUR and ANDROCUR DEPOT come in the following dosage forms:

ANDROCUR Tablet: Each tablet contains 50 mg cyproterone acetate

ANDROCUR DEPOT Solution: Each 3 mL ampoule contains 100 mg/mL cyproterone acetate

Do not use ANDROCUR and ANDROCUR DEPOT if you:

- are allergic (hypersensitive) to cyproterone acetate or any of the other ingredients of ANDROCUR and ANDROCUR DEPOT;
- have a liver disease or reduced liver function;
- have Dubin-Johnson syndrome or Rotor syndrome. Both syndromes result in an increase in bilirubin (red blood cell pigment);
- have or have had liver tumors that are not due to the spread of prostate cancer;
- have or ever had a benign brain tumor (meningioma);
- have wasting diseases (diseases involving an unintended loss of weight or muscle) that are not related to prostate cancer;
- suffer from severe chronic depression;
- have conditions that increase your risk for developing blood clots (thromboembolic process).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ANDROCUR and ANDROCUR DEPOT. Talk about any health conditions or problems you may have, including if you:

- have a breathing problem. Shortness of breath has been reported in patients taking 300 mg a day of ANDROCUR.
- have heart disease;
- have blood clots. Blood clots have been reported in patients taking ANDROCUR and ANDROCUR DEPOT. Tell your doctor if any of the following apply to you, as you may be at an increased risk of getting a blood clot. If you have:
    - a history of blood clots, strokes or heart attacks
    - cancer
    - abnormal red blood cells (sickle-cell anaemia)
    - Severe diabetes that affects your blood circulation
- have liver problem. Severe and fatal liver problems have been reported with ANDROCUR and ANDROCUR DEPOT. Your doctor may conduct regular liver tests before and during treatment to monitor the condition of your liver. Your doctor might decide to end your treatment if necessary;
- have or have had a history of depression;
- have diabetes. Your doctor may need to adjust your antidiabetic medication as taking ANDROCUR and ANDROCUR DEPOT can alter the sugar levels in your blood. Your doctor will check your blood sugars before you begin and during treatment. Strict supervision is required if you are diabetic during your treatment.
- have anemia. Your doctor will monitor your red-blood cell count during treatment. Anaemia has been reported rarely during long term treatment with ANDROCUR and ANDROCUR DEPOT;
- have a history of benign brain tumors (meningiomas).

Other warnings you should know about:

ANDROCUR and ANDROCUR DEPOT is not for use in:

- women
- children under the age of 18

- males who have not reached the end of puberty. Using it may have a negative effect on growth and hormonal functions.

Alcohol use:

Consuming alcohol while taking ANDROCUR and ANDROCUR DEPOT may impact the effect of the drug. It is recommended that you avoid the use of alcohol while on treatment.

Use with orchiectomy or GnRH agonist drugs

Your life expectancy may be reduced if you are taking ANDROCUR and ANDROCUR DEPOT for a long period of time if you:

- had an orchiectomy (removal of testicles) or;
- are taking a GnRH agonist (one class of drug that acts against male sex hormones).

Long term treatment in patients with advanced prostate cancer may reduce the life expectancy by 5 years when compared to using surgical castration treatment only.

Driving and using machines:

You may feel tired and weak during treatment. Before you do tasks that require special attention, wait until you know how your body responds to ANDROCUR and ANDROCUR DEPOT.

Pulmonary oil microembolism and post-injection reactions

ANDROCUR DEPOT needs to be injected very slowly into the muscle to prevent:

- pulmonary oil microembolism (when oily solution gets into the lung). Pulmonary microembolism can cause symptoms such as coughing, shortness of breath and chest pain. And;
- vasovagal reactions (post-injection reactions). Vasovagal reactions can cause symptoms such as discomfort, bleeding, dizziness, tingling or pricking sensation, or fainting.

Liver tumours (benign and malignant)

Using medicines such as ANDROCUR has very rarely been linked to the development of:

- benign (non-malignant) liver tumours and;
- some forms of liver cancer (malignant liver tumours).

Benign brain tumours (meningiomas)

You may develop meningioma if you take ANDROCUR for a long duration. Meningioma has been rarely reported in patients with prostate cancer that are taking ANDROCUR for a shorter duration. Your risk increases especially when you use it for a longer duration (several years) or for a shorter duration with high doses (25mg per day and above). If you are diagnosed with meningioma, your doctor will stop your treatment.

Antiandrogen Withdrawal Syndrome

Taking ANDROCUR and ANDROCUR DEPOT may increase the risk of the prostate cancer growing, rather than prevent it. Your doctor will stop your treatment immediately and monitor your condition for 6-8 weeks before deciding to proceed with other prostate cancer therapies.

Swelling of breast tissue in males

You may experience swelling of your breasts while on treatment. Your doctor may reduce your dosage or terminate your treatment once assessing your condition.

Adrenal glands

Your adrenal glands may become supressed during treatment with ANDROCUR and ANDROCUR DEPOT. Your doctor will check the function of your adrenal glands periodically.

Sperm count:

Your sperm count and the amount of ejaculation is reduced when taking 50 mg to 300 mg of ANDROCUR a day. Your sperm count and ejaculation will usually return to normal after stopping your treatment.

Skin

Treatment with ANDROCUR and ANDROCUR DEPOT may cause the following skin problems:

- Dry skin
- Patchy body hair loss

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ANDROCUR and ANDROCUR DEPOT:

- 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)

How to take ANDROCUR and ANDROCUR DEPOT:

- Take exactly as your doctor tells you to take it. Do NOT take more of it than prescribed. Check with your doctor if you are not sure.
- Do not reduce your dose or stop taking your medicine unless your doctor tells you to.

Usual adult dose:

ANDROCUR Tablet

The recommended starting and maintenance daily dose: 200 mg to 300 mg (4 to 6 tablets) taken in two or three divided doses. Each dose should be taken with liquid after meals.

The maximum daily dose: 300 mg.

Recommended daily dose after orchiectomy (removal of testicles): 100-200 mg (2 to 4 tablets).

ANDROCUR DEPOT Injection

The recommended starting and maintenance dose: 300 mg (3 mL) once a week. ANDROCUR DEPOT is to be given slowly into a muscle (intramuscular).

Recommended dose after orchiectomy (removal of testicles): 300 mg (3 mL) once every two weeks.

Overdose:

If you think you, or a person you are caring for, have taken too much ANDROCUR or ANDROCUR DEPOT, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

ANDROCUR Tablet

If you missed a dose of ANDROCUR tablet, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

ANDROCUR DEPOT Injection

Have a new appointment with your doctor in order to make up for the forgotten injection. You should not get a double dose.

What are possible side effects from using ANDROCUR and ANDROCUR DEPOT?

These are not all the possible side effects you may feel when taking ANDROCUR. If you experience any side effects not listed here, contact your healthcare professional.

Very frequent side effects:

- Swelling of the breast, breast soreness (gynecomastia)

Other side effects:

- Constipation or diarrhea (loose stools)
- Depression
- Dizziness
- Fever or chills
- Frequent urination
- Hair loss or unusual increase in hair growth
- Headache
- Hot flashes
- Indigestion
- Nausea
- Shortness of breath
- Skin rash, blisters
- Skin discoloration
- Tiredness and weakness
- Unusual swelling of the arms, hands, legs, feet and ankles, face
- Vomiting

- Vision change
- Weight gain or weight loss

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Inability to achieve or maintain and erection	✓		
Reduced sexual drive	✓		
Reversible inhibition of sperm production	✓		
RARE			
Liver toxicity, liver inflammation (hepatitis), liver disease, liver failure: 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			✓
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)			✓
Life-threatening internal bleeding (intra-abdominal hemorrhage): unusual upper abdominal pains which do not disappear within a short time			✓
UNKNOWN			

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Osteoporosis (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking		✓	
Pulmonary oil microembolism (oily solution gets into the lung): cough, shortness of breath, or chest pain		✓	
General post injection reactions (vasovagal reactions): malaise, increased sweating, dizziness, "pins and needles" sensation or fainting		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Benign brain tumors: dull and constant headaches, seizures, sensory deficits (hearing or vision problems, loss of coordination or spatial orientation), cognitive dysfunction (difficulty concentrating, mood or personality problems), and increased intracranial pressure (presents as nausea, headache, papilledema)		✓	
Galactorrhea (production of breast milk): nipple discharge in one or both breasts, headaches, vision problems		✓	
Benign (not cancer) breast lump: pain, swelling and/or tenderness		✓	

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
in the breast, skin irritation, nipple pain, feeling of a lump through the skin or nipple, redness or scaling on the nipple, and nipple pain or retraction			
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Allergic reaction: hypersensitivity, itchiness, rash, swelling, difficulty breathing			✓
Asthma: difficulty breathing and coughing, chest tightness, wheezing or whistling sound when breathing			✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen		✓	
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Diabetes or increase in blood sugar: with symptoms such as excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections		✓	

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not take ANDROCUR after the expiry date which is stated on the pack.

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

Keep out of reach and sight of children.

If you want more information about ANDROCUR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

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