

rare cases hepatic tumors may cause life-threatening intra-abdominal hemorrhage. Therefore, the physician should be told if unusual epigastric disorders occur and they do not disappear by themselves short afterwards. Patients with diabetes should be carefully monitored by the physician. Antidiabetics or insulin requirements may also be modified.

#### MONITORING OF PATIENTS:

During treatment, hepatic function, adrenocortical function, and red blood cell count should be checked regularly. Before commencing treatment in women, a thorough gynecological examination (including the breasts and cervical cytological smear) should be carried out. In women of childbearing potential, pregnancy must be excluded.

If a slight unscheduled bleeding occurs during the 3 weeks of a combined treatment including an estrogen-gestagen combination preparation, treatment should not be discontinued. Only if bleeding becomes heavier medical attention should be sought.

#### ADVERSE REACTIONS:

In men, sexual ability is gradually reduced during the first weeks of treatment. Some months after treatment is completed, this ability returns to its initial status. Occasionally, gynecomastia has been reported in male patients, sometimes associated with tactile mammillary hypersensitivity. These manifestations generally remit upon treatment discontinuation. In women under a combined treatment, ovulation is inhibited; so, infertility exists. A sensation of tension in the breasts may occur.

Severe disturbance of liver function have been rarely reported with high-dose cyproterone acetate treatment.

Tiredness, adynamia, inner restlessness, and depressive moods may occur in any type of patient. Changes in body weight are also likely to occur.

In occasions, cyproterone acetate may cause dyspnea.

Thromboembolic phenomena have been very rarely reported in patients receiving cyproterone acetate. However, the connection between these phenomena and cyproterone is uncertain.

#### STORE BETWEEN 15 °C AND 30 °C AND PROTECT FROM LIGHT.

#### PRESENTATION:

Ciproterona Servycal 50 mg x 50 tablets.

**In the event of overdosage, go to the nearest Hospital**

#### KEEP OUT OF REACH OF CHILDREN

**This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.**

Medicinal Specialty authorized by the Argentine Ministry of Health (ANMAT). Certificate No. 49.671.

#### SERVYCAL S.A.

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## **Ciproterona Servycal** **Cyproterone Acetate 50 mg** Tablets

Sale under filed prescription  
Made in Argentina

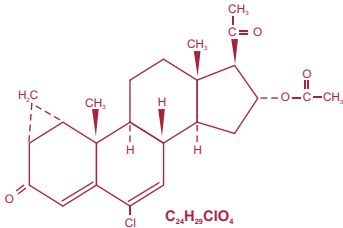
Any medicine having cyproterone acetate as its active ingredient may produce the effects mentioned below.

Cyproterone acetate must only be administered by an oncologist.

#### QUALI-QUANTITATIVE COMPOSITION:

Each tablet contains:  
Cyproterone acetate 50.00 mg  
Lactose 160.00 mg  
Talc 1.00 mg  
Magnesium stearate 1.25 mg  
Microcrystalline Cellulose PH 102 15.00 mg  
Corn starch 24.00 mg

#### CHEMICAL STRUCTURE:



#### DRUG CATEGORY AND ACTION:

ATC Classification: G03H A01  
Antiandrogen.

Cyproterone acetate inhibits the action of male sex hormones (androgens) which, to a lesser extent, are also present in females. It also exerts a gestagenic and antigonadotrophic action. In male patients, treatment with cyproterone acetate reduces sexual drive and potency, and inhibits gonadal function.

These changes are reversible upon discontinuation of treatment.

Cyproterone acetate protects androgen dependent target organs, such as the prostate, against the effect of gonadal and/or adrenocortical androgens.

In women, hirsutism is diminished, but also androgen dependent loss of hair and elevated sebaceous gland function are reduced. During treatment, ovarian function is inhibited.

#### INDICATIONS:

Cyproterone acetate is indicated:

- For the antiandrogenic treatment of hormone-dependent inoperable prostatic carcinoma.
- To diminish the initial increase of male sex hormones in the treatment with LHRH agonists.
- To preclude the effect of adrenocortical androgens in the treatment with LHRH agonists.
- For the treatment of severe signs of androgenization in women, such us excessive and pathological hair growth in the face and body (severe hirsutism) and marked hair loss to baldness (severe androgenic alopecia), usually associated with acne and/or seborrhea.
- For the reduction of drive in male sexual deviations.
- For the treatment of postmenopausal or hysterectomized women with cyproterone acetate as single agent.

#### PHARMACOKINETICS:

Cyproterone acetate is absorbed from the gastrointestinal tract. Peak plasma levels are reached 3 to 4 hours following administration and fall quickly up to 24 hours following administration due to tissue distribution and elimination. Plasma half-life is 38 hours. It is excreted in the feces, in the urine in the form of unconjugated drug and metabolites: the main metabolite being the 15β-hydroxycyproterone acetate.

#### DOSAGE AND ADMINISTRATION:

- For the antiandrogenic treatment of hormone-dependent inoperable prostatic carcinoma:
  - To preclude the effect of adrenal androgens after orchiectomy: 2 tablets of 50 mg, once to twice a day (100/200 mg).
  - In non-orchiectomized patients: 2 tablets of 50 mg, twice to three times a day (200/300 mg).
- Tablets should be taken with some liquid after meals. If improvement or remission occurs, the dose prescribed by the physician should not be modified nor should therapy be discontinued.

- To diminish the initial increase of male sex hormones in the treatment with LHRH agonists:
  - Initially, 2 tablets of 50 mg for 5 to 7 days, twice a day (200 mg). Then, 2 tablets of 50 mg for 3 to 4 weeks, twice a day, in combination with a LHRH agonist at the dose recommended by the manufacturer.

- To preclude the effect of adrenocortical androgens in the treatment with LHRH agonists:
  - Continue antiandrogenic treatment with 2 tablets of 50 mg, once to twice a day (100/200 mg).

- For the reduction of drive in male sexual deviations:
  - Dosage shall be determined by physician. Tablets should be taken with some liquid after meals. The initial dose is generally 1 tablet of 50 mg, twice a day (100 mg). It may be necessary to increase the dose temporarily to two tablets twice daily or even three times daily (200/300/mg). Once a satisfactory result is achieved, the therapeutic effect should be maintained with the lowest possible dose; often half a tablet twice a day (50 mg) is enough.

When establishing the maintenance dose or even discontinuing treatment, the dosage should not be reduced abruptly, but gradually, for which purpose the daily dose should be reduced by half a tablet (25 mg), at intervals of several weeks.

To stabilize the therapeutic effect is necessary to take cyproterone acetate over a longer period of time, if possible with the simultaneous application of psychotherapeutic measures.

- Dosage and use in women:
  - Pregnant women must not take cyproterone acetate. Before commencing treatment, pregnancy should be ruled out.

In women of childbearing potential with severe signs of androgenization, such us excessive and pathological hair growth in the face and body (severe hirsutism) and marked hair loss to baldness (severe androgenic alopecia), usually associated with acne and seborrhea, treatment is commenced on the first day of the menstrual cycle. Only patients with amenorrhea will start treatment immediately, following the therapeutic scheme that follows, as if the first day of treatment would have coincided with the first day of the cycle: from day 1 to 10 of the cycle (for 10 days), 2 tablets of 50 mg should be taken daily with some liquid after meals. In parallel with this regime, and in order to stabilize the cycle and provide the necessary contraceptive protection, these patients should receive an estrogen-gestagen combination preparation, at a dose of 1 tablet a day from day 1 to 21 of the cycle (for 21 days).

Women receiving the cyclical combined therapy should take their contraceptive tablets at the same time each day. If a tablet is missed and more than 12 hours elapse from the missing tablet, the contraceptive protection is no longer effective during the corresponding cycle. Nevertheless, both medicines should be continued as instructed, ignoring the missed tablet, in order to avoid premature bleeding due to deprivation during this cycle.

In addition, other nonhormone contraceptive methods should be employed (except for the rhythm -like the Ogino-Knaus- or the temperature methods) until the end of the cycle.

After 21 days of treatment, a 7-day break is made during which a bleeding occurs that is similar to menstruation. Four weeks after the first day of treatment and on a day coinciding with the same day of the week, combined treatment is resumed according to the same scheme, regardless of whether bleeding has stopped or not. If no bleeding occurs during the 7-day break, patient should consult her doctor. Once clinical improvement is attained, the daily dose of cyproterone acetate may be reduced by physician to 1 tablet or half a tablet for the first 10 days of combined treatment with the estrogen-gestagen combination preparation. Whenever a cyclical combined treatment with cyproterone acetate and an estrogen-gestagen combination preparation is used, the instructions and warnings included in the patient package insert of said combination preparation should also be observed.

- For the treatment of postmenopausal or hysterectomized women with cyproterone acetate as single agent:

According to the severity of the disturbances, the dose should be half to 1 tablet of 50 mg once daily for 21 days followed by a 7-day break in treatment.

1	Days	7	8	10	14	15	Days	21	7 days break
X	X	X	X	X	X	X			
X	X	X	X	X	X	X			Bleeding
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

#### References:

X: Ciproterona Servycal tablet.  
Y: estrogen-gestagen combination.

Because cyproterone acetate is a potent progestogen and a moderate antiandrogen, it is used in low daily doses of 2 mg as an oral contraceptive (combined with estrogens).

Cyproterone acetate may also be administered uninterruptedly to hysterectomized women at a daily

dose of 25 mg.

Besides, this dose may be used in women with polycystic ovary syndrome with increased plasma testosterone levels.

#### CONTRAINDICATIONS/MEDICAL PROBLEMS:

Cyproterone acetate is contraindicated in the following cases:

Pregnancy, lactation, acute and chronic hepatic diseases, jaundice or severe itching during a previous pregnancy, a history of herpes of pregnancy, Dubin-Johnson syndrome, Rotor syndrome, previously treated or existing hepatic tumors (in carcinoma of the prostate only if these are not due to metastases), wasting diseases (except for inoperable carcinoma of the prostate), severe chronic depressions, previous or existing thromboembolic processes, severe diabetes with vascular changes, sickle-cell anemia, breast carcinoma, congenital or existing disorders of fat metabolism.

In prostatic carcinoma patients with a history of thromboembolic processes, severe diabetes with vascular changes, and sickle-cell anemia, the risk-benefit ratio should be assessed.

Whenever a combined cyclical treatment with cyproterone acetate and an estrogen-gestagen combination preparation is used to treat signs of androgenization in women, the contraindications included in the patient package insert of the combination preparation should also be observed.

#### PRECAUTIONS:

Patients whose occupation require great concentration, such as vehicle drivers, road users or machine operators, should be warned that cyproterone acetate may lead to tiredness and adynamia, thus affecting the ability to concentrate.

Cyproterone acetate should not be given before puberty since a negative influence on longitudinal growth and the still unstabilized self-regulatory endocrine system cannot be ruled out.





Before commencing treatment, a thorough gynecological examination should be carried out and pregnancy must be excluded.

#### DRUG INTERACTIONS AND/OR RELATED PROBLEMS:

The use of alcohol may diminish the sexual drive reduction effect of cyproterone acetate.

As with other sex steroids, cases of benign and malignant hepatic tumors have been rarely reported. In

71020-02

PRODUCTO: Ciproterona Servycal - Ingles - Prospecto			VERSION - 02.1		
COLORES	ALTERACIONES	Código Actual: 71020-02			
 Pantone 194	<b>Emisión inicial:</b> Actualización de textos y nuevo DT.		Aprobado por:	Fecha	
	Código anterior: 71020		Desarrollo de Packaging		
	Medida: 220 x 140 ± 1 mm	 Trazado	Director Técnico		
	Fuentes: <b>Frutiger Black Italic</b> – Arial (resto del texto)		Garantía de Calidad		
<b>Material:</b> Papel Chambril 56 g/m <sup>2</sup> ± 5%.					