

BICALUTAMIDA SERVYCAL

BICALUTAMIDE 50 mg

TABLETS

SALE UNDER FILED PRESCRIPTION

MADE IN ARGENTINA

Any medicine having bicalutamide as active ingredient may produce the effects mentioned below.

Bicalutamide must only be administered by a physician specialized in the use of this type of medicine.

QUALI-QUANTITATIVE COMPOSITION:

Each tablet of Bicalutamida Servycal 50 mg contains:

Bicalutamide	50.0 mg
Lactose	61.0 mg
Sodium starch glycollate	7.5 mg
Povidone	5.0 mg
Magnesium stearate	1.5 mg

CATEGORY:

Antineoplastic. ATC classification: L02B B03

DESCRIPTION:

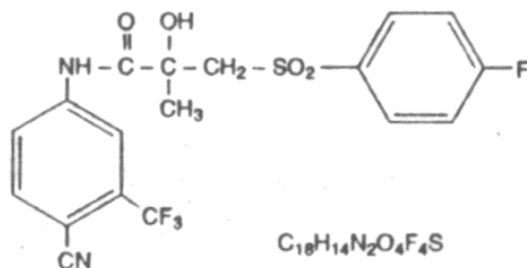
Bicalutamida Servycal, tablets, contains 50 mg of bicalutamide, a non-steroidal antiandrogen with no other endocrine activity.

Bicalutamide has a molecular weight of 430.37. The pka is approximately 12.

Bicalutamide is a white to off-white powder, practically insoluble in water (5 mg/L at 37° C), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

Bicalutamide is a racemate whose antiandrogenic activity is almost exclusively exhibited by R-enantiomer; the S-enantiomer is essentially inactive.

Chemical structure:



INDICATIONS:

Bicalutamide is indicated in combination with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of stage D2 metastatic carcinoma of the prostate.

PHARMACOLOGY:

Pharmacological action:

Mechanism of action: bicalutamide is a non-steroidal antiandrogen. It inhibits competitively the action of androgens by binding to cytosol androgen receptors in the target tissue. It is known that prostatic carcinomas are androgen sensitive and respond to treatments which counteract the effects of androgens and/or remove the source of androgens.

In clinical trials with bicalutamide as single agent for the treatment of prostate cancer, rises in serum testosterone or estradiol have not been observed.

When bicalutamide is combined with luteinizing hormone-release hormone analogue (LHRH), the suppression of testosterone induced by LHRH analogue is not affected.

Pharmacokinetics:

Absorption: although bicalutamide is well absorbed after oral administration, the absolute bioavailability is unknown.

Bicalutamide administration together with food has no effect on rate or extent of absorption.

Distribution: bicalutamide is highly protein-bound (96%).

Metabolism/elimination: bicalutamide undergoes stereospecific metabolism. The S isomer (inactive) is metabolized primarily by glucuronidation. The R isomer (active) also undergoes glucuronidation but it is mainly oxidized to an inactive metabolite and then glucuronidated. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S enantiomer is rapidly eliminated relative to R enantiomer.

Of steady-state plasma levels, 99% of bicalutamide corresponds to R enantiomer.

Special populations

Geriatric: in two studies in patients given 50 or 150 mg/day, no relationship between age and plasma levels of total bicalutamide or the R enantiomer has been noted.

Hepatic insufficiency: No clinically significant difference in the pharmacokinetics of bicalutamide enantiomers was noted in patients with mild-to-moderate hepatic disease as compared to patients with normal hepatic function. In patients with severe hepatic disease, the half-life of the R enantiomer was significantly increased.

Renal insufficiency: renal insufficiency (measured by creatinine clearance) has no significant effect on the elimination of bicalutamide or its active R enantiomer.

Women, children: Because of its mechanism of action and indications, bicalutamide has not been studied in women or children.

Drug-drug interactions: studies have shown no interaction between bicalutamide or LHRH analogue and other drugs.

There is no evidence that bicalutamide induces hepatic enzymes. *In vitro* protein-binding studies have shown that bicalutamide may displace coumarin anticoagulants from binding sites. Prothrombin times should be monitored in patients treated with coumarin anticoagulants who also receive Bicalutamida Servycal.

Table 1 includes the pharmacokinetics of the active enantiomer of bicalutamide in normal males and patients with prostate cancer.

Parameter	Average	CV %	95 % Confidence interval
<u>Normal males (n=30)</u>			
Aparent oral clearance (L/h)	0.320	32.1	0.281 – 0.358
Peak concentration following single dose (µg/mL)	0.768	23.2	0.702 – 0.835
Time to peak concentration following single dose (hours)	31.3	46.5	25.9 – 36.7
Half-life (days)	5.8	39.5	4.9 – 6.7
<u>Patients with prostate cancer (n=40)</u>			
Steady-state plasma concentration (µg/mL)	8.939	39.2	7.817 – 10.06

CV = coefficient of variation

DOSAGE AND ADMINISTRATION

The recommended dose of Bicalutamida Servycal in combination with an LHRH analogue is one 50-mg tablet once daily (morning or evening), with or without food.

Bicalutamida Servycal should be taken at the same time each day.

Treatment with Bicalutamida Servycal should start at the same time as treatment with LHRH analogue.

CONTRAINDICATIONS

Bicalutamide is contraindicated in patients who have shown a hypersensitivity reaction to the drug or to any of its components.

Bicalutamide may cause fetal harm if it is given to pregnant women.

The male offspring of rats receiving 10 mg/kg/day (plasma concentrations equal to 2/3 of human therapeutic concentrations) and greater doses, showed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These effects have also been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 250 mg/kg/day (approximately 2 times human therapeutic dose).

Bicalutamide is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant during treatment, the patient should be advised of the potential hazard to the fetus.

WARNINGS

In clinical trials with bicalutamide as single agent for the treatment of prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

PRECAUTIONS

Bicalutamide should be used with caution in patients with moderate-to-severe hepatic impairment. Bicalutamide is extensively metabolized in the liver.

Limited data in patients with severe hepatic impairment suggest that the excretion of bicalutamide may be delayed and may lead to further accumulation. The liver function of patients with hepatic impairment who are on long-term therapy should be tested on a regular basis.

Information for patients: patients should be informed that therapy with bicalutamide and the LHRH analogue should be started concomitantly, and that they should not be interrupt or stop taking them without consulting their physician first. Treatment with bicalutamide should be initiated at the same time as the treatment with an LHRH analogue.

Laboratory tests: in order to monitor patient's response, it may be helpful to perform regular tests of prostate specific antigen (PSA). If PSA levels rise during bicalutamide therapy, the patient should be evaluated for clinical progression.

In the case of patients who have objective progression of the disease as well as elevated PSA, a treatment-free period of antiandrogen should be considered, while continuing the LHRH analogue.

Because hepatic abnormalities, and, rarely, jaundice have been reported, periodic liver function tests should be considered. Bicalutamide therapy should be discontinued if there are clinical signs suggestive of any of these diseases, for example if the patient has jaundice or if there is laboratory evidence of liver injury in the absence of liver metastasis. If transaminases increase over 2 times the upper limit of normal, treatment should be discontinued. Abnormalities are reversible upon treatment discontinuation.

Drug-drug interactions: *In vitro* studies have shown that bicalutamide may displace coumarin anticoagulants, like warfarin, from their protein-binding site. Prothrombin times should be monitored in patients treated with coumarin anticoagulants who also receive Bicalutamida Servycal, and anticoagulant dose should be adjusted if necessary.

Carcinogenesis, mutagenesis and impairment of fertility: Two-year studies were conducted in both male and female rats and mice at doses of 5, 15, or 75 mg/kg/day of bicalutamide. A variety of tumor in target organs was identified and attributed to the antiandrogenic effect of bicalutamide, which variety is called testicular benign interstitial (Leydig) cell tumor, in male rats at all dose levels (steady-state plasma concentration with the 5 mg/kg/day dose is approximately 2/3 of human therapeutic concentrations). Uterine adenocarcinoma was found in female mice at 75 m/kg/day of bicalutamide (approximately 1.5 times the human therapeutic concentrations).

There is no evidence of Leydig cell hyperplasia in patients. Uterine tumors are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice receiving 75 mg/kg/day (approximately 4 times human therapeutic concentrations) and an increase in the incidence of benign thyroid follicular cell adenoma in rats receiving 5 mg/kg/day (approximately 2/3 times human therapeutic concentrations) or greater doses were recorded.

These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies.

Enzyme induction has not been observed after bicalutamide administration in humans. There were no tumorigenic effects suggestive of genotoxic carcinogenesis.

A complete battery of both in vitro and in vivo tests (yeast gene conversion, Ames, E. coli, CHO/HGPRT, human lymphocyte cytogenic, mouse micronucleus, rat bone marrow cytogenetic tests) has shown that bicalutamide has no genotoxic activity.

Bicalutamide administration may inhibit spermatogenesis.

The long-term effects of bicalutamide on male fertility have not been studied.

No effect was observed in female rats, or their offspring, given 10, 50 and 250 mg/kg/day of bicalutamide (approximately 2/3, 1 and 2 times human therapeutic concentrations). The administration of bicalutamide to pregnant female rats produced the feminization of male offspring, leading to hypospadias at all dose levels. The affected male offspring were also impotent.

Pregnancy: Pregnancy category X.

Breastfeeding: It is unknown whether bicalutamide is excreted in breast milk.

Because many drugs are excreted in breast milk, women receiving bicalutamide should avoid breastfeeding.

Pediatric use: Safety and effectiveness of bicalutamide in pediatric patients have not been established.

ADVERSE REACTIONS

In patients with advanced prostate cancer treated with bicalutamide plus an LHRH analogue, the most frequent adverse effect was hot flashes (49%).

The adverse effect that most frequently led to treatment withdrawal was diarrhea: 6% of patients treated with flutamide-LHRH analogue and 0.5% of patients treated with bicalutamide- LHRH analogue.

In a multicenter, double-blind, controlled clinical trial comparing bicalutamide 50 mg once daily with flutamide 250 mg three times a day, both of them in combination with an LHRH analogue, the following adverse effects have been reported with an incidence of 5% or greater, regardless of causality:

Incidence of adverse effects $\geq 5\%$ in any treatment group

Adverse effects	Bicalutamide – LHRH analogue n = 401		Flutamide – LHRH analogue n = 407	
	n	%	n	%
Body (general)				
Pain (general)	109	27	93	23
Back pain	62	15	68	17
Asthenia	60	15	69	17
Pelvic pain	52	13	46	11
Infection	41	10	35	9
Abdominal pain	33	8	31	8
Chest pain	24	6	20	5
Headache	17	4	20	5
Flu syndrome	16	4	20	5
Cardiovascular				
Hot flashes	196	49	202	50
Hypertension	21	5	18	4

Digestive				
Constipation	67	17	50	12
Nausea	44	11	45	11
Diarrhea	40	10	98	24
Increased liver enzyme	25	6	40	10
Flatulence	22	5	16	4
Hemic and lymphatic				
Anemia	29	7	35	9
Metabolic and nutritional				
Peripheral edema	34	8	24	7
Hyperglycemia	20	5	16	4
Weight loss	16	4	20	5
Musculoskeletal				
Bone pain	18	4	26	6
Nervous system				
Dizziness	30	7	27	7
Paresthesia	24	6	27	7
Insomnia	19	5	30	7
Respiratory system				
Dyspnea	30	7	24	6
Skin and appendages				
Rash	25	6	20	5
Sweating	23	6	18	4
Urogenital				
Nocturia	35	9	43	11
Hematuria	30	7	20	5
Urinary tract infection	26	6	24	6
Impotence	20	5	29	7
Gynecomastia	19	5	23	6
Urinary incontinence	9	2	20	5

There follows a list of less frequently reported adverse effects (less of 5% but more than 2%) in bicalutamide treatment, regardless of causality. Some of them are usually reported in elderly patients.

Body (general): edemas, neoplasm, fever, neck pain, chills, sepsis.

Cardiovascular: angina pectoris, congestive heart failure.

Digestive: anorexia, dyspepsia, rectal hemorrhage, dry mouth.

Endocrine: breast pain, diabetes mellitus.

Metabolic and nutritional: increased phosphatase alkaline, weight gain, increased creatinine, dehydration, gout.

Musculoskeletal: myasthenia, arthritis, myalgia, leg cramps, pathological fracture.

Nervous: anxiety, depression, decreased libido, hypertonia, somnolence, confusion, neuropathy, nervousness.

Respiratory: increased cough, pharyngitis, bronchitis, pneumonia, rhinitis, pulmonary disorders.

Skin and appendages: dry skin, alopecia.

Urogenital: increased urinary frequency, urinary impairment, dysuria, urinary retention, urinary urgency.

Abnormal laboratory test values: In both treatment groups, namely bicalutamide-LHRH analogue and flutamide-LHRH, abnormal laboratory test values were reported, including elevated AST, ALT, bilirubin, BUN, and creatinine, and decreased hemoglobin and WBC. Elevated hepatic enzymes and decreased hemoglobin were less frequently reported in the bicalutamide group. The other changes had a similar incidence in both groups.

OVERDOSAGE

In animal studies bicalutamide has shown to have low acute toxicity. Doses greater than 2000 mg/kg/day were necessary to cause significant mortality in rats and mice.

Long-term clinical trials have been conducted with doses of 200 mg of bicalutamide daily and these doses have been well tolerated. The single dose of bicalutamide that results in overdose symptoms considered to be life-threatening has not been established.

If an overdose occurs, go to the nearest Hospital or contact Toxicology Centers:

Hospital de Niños Dr. Ricardo Gutiérrez: Ph: + 54 (11) 4962-6666 / 2247

Hospital Dr. Juan P. Garrahan: Ph: + 54 (11) 4941-6191 / 6012

Hospital Dr. Juan A. Fernández: Ph: + 54 (11) 4801-5555

Hospital A. Posadas: Ph: + 54 (11) 4654-6648 / 4658-7777

There is no specific antidote, treatment should be symptomatic.

In the event of an overdose with bicalutamide, vomiting should be induced if patient is conscious. It should be taken into account that this type of patient may have taken multiple drugs. As bicalutamide is highly protein bound and it is extensively metabolized, dialysis is

not likely to be helpful. Patient should be observed, including frequent monitoring of vital signs, and general supportive treatment should be provided.

PRESENTATION:

BICALUTAMIDA SERVYCAL 50 mg x 28 tablets.

STORAGE: Store between 15° C and 30° C, protected from moisture.

KEEP OUT OF REACH OF CHILDREN

This medicine shall be used under medical prescription and it shall not be repeated without a new prescription.

Medicinal Specialty authorized by the Argentine Ministry of Health (A.N.M.A.T.)-
Certificate No. 49488:

Technical Director: Pamela Carla Marcuzzi – Pharmacist- Biochemist

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