PRODUCT MONOGRAPH

[Pr]BICALUTAMIDE

Bicalutamide Tablets

50 mg

Non-Steroidal Antiandrogen

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H4P 2T4

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Bicalutamide Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Tablet 50 mg	colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethelyne glycol, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, triethyl citrate

INDICATIONS AND CLINICAL USE

BICALUTAMIDE (bicalutamide) 50 mg is indicated for use in combination therapy with either an LHRH analogue or surgical castration in the treatment of metastatic (Stage D2) prostate cancer.

Pediatrics:
The safety and effectiveness of bicalutamide in children has not been established.

CONTRAINDICATIONS

BICALUTAMIDE (bicalutamide) is contraindicated in the following:

- Patients who are hypersensitive to the drug or any of its components. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Patients with localized prostate cancer otherwise undergoing watchful waiting. (see WARNINGS AND PRECAUTIONS)
- Women: The safety and effectiveness of bicalutamide in women has not been studied.
- Children: The safety and effectiveness of bicalutamide in children has not been

studied.

WARNINGS AND PRECAUTIONS

BICALUTAMIDE (bicalutamide) should only be prescribed by a qualified healthcare professional who is experienced with the treatment of prostate cancer and the use of anti-androgens.

- BICALUTAMIDE 150 mg/day dose should not be used (see WARNINGS & PRECAUTIONS, General).
- Rare hepatic failure, including fatal outcomes (see WARNINGS & PRECAUTIONS, Hepatic).
- Uncommon interstitial lung disease, including fatal outcomes (see WARNINGS & PRECAUTIONS, Respiratory).

General

During treatment with bicalutamide, somnolence has been reported and those patients who experience this symptom should observe caution when driving or using machines.

Localized Prostate Cancer patients

Bicalutamide 150 mg is NOT to be administered.

Evidence from a large on-going clinical study demonstrates that at 5.4 year median follow-up, the use of bicalutamide 150 mg as immediate therapy for the treatment of localized prostate cancer in patients otherwise undergoing watchful waiting is associated with increased mortality. Health Canada previously assessed bicalutamide 150 mg versus castration in the locally advanced patient population and found level 1 scientific evidence (one of the 2 randomized clinical trials) of increased mortality in bicalutamide 150 mg treated patients.

Patients taking bicalutamide 50 mg per day for the treatment of metastatic prostate cancer are not affected by this new information.

Anti-androgen Withdrawal Syndrome

In some patients with metastatic prostate cancer, anti-androgens (steroidal and non-steroidal), may promote, rather than inhibit, the growth of prostate cancer. A decrease in PSA and/or clinical improvement following 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 6-8 weeks for a withdrawal response prior to any decision to proceed with other prostate cancer therapy.

Cardiovascular

Bicalutamide is indicated for use in combination with either an LHRH analogue or surgical castration. Combined androgen blockade with an anti-androgen plus LHRH analogue or surgical castration increases risk of cardiovascular disease (heart attack, cardiac failure, sudden cardiac death) and adversely affects independent cardiovascular risk factors (serum lipoproteins, insulin sensitivity and obesity). Physicians should carefully consider whether the benefits of combined androgen blockade outweigh the potential cardiovascular risk. Assessment of cardiovascular risk factors, monitoring for signs and symptoms suggestive

of development of cardiovascular disease, and management according to local clinical practice and guidelines should be considered.

Effect on QT/QTc interval
Bicalutamide is indicated for use in combination with either an LHRH analogue or surgical castration. Combined androgen blockade with an anti-androgen plus LHRH analogue or surgical castration has the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of combined androgen blockade outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications.

Endocrine and Metabolism
A reduction in glucose tolerance and/or glycated hemoglobin (HbAlc) has been observed in males receiving bicalutamide in combination with LHRH analogues. This may manifest as diabetes or loss of glycemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose and/or glycated hemoglobin (HbAlc) in patients receiving bicalutamide in combination with LHRH analogues.

Gynaecomastia, Breast Pain
Gynaecomastia has been reported in patients receiving bicalutamide. For metastatic (M1) patients receiving bicalutamide 50 mg, concomitant surgical or medical castration may reduce the effects of gynaecomastia.

Hematologic
Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Hepatic
Bicalutamide is extensively metabolized in the liver. Data suggests that the elimination of bicalutamide may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Hepatotoxicity including rare hepatic failure has been observed with bicalutamide, and fatal outcomes have been reported. Bicalutamide therapy should be discontinued if changes are severe (also see Post-Market Adverse Drug Reactions).

Musculoskeletal
Changes in Bone Density

Bicalutamide is indicated for use in combination with either an LHRH analogue or surgical castration. Decreased bone mineral density can be anticipated with long term combined androgen blockade with an anti-androgen plus LHRH analogue or surgical castration. Combined androgen blockade is associated with increased risks of osteoporosis and skeletal

bone fractures. The risk of skeletal fracture increases with the duration of combined androgen blockade. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, combined androgen blockade may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before combined androgen blockade is instituted.

Respiratory

Uncommon cases of interstitial lung disease (some cases have been fatal) have been reported with bicalutamide (also see Post-Market Adverse Drug Reactions). Interstitial lung disease has been reported most often at doses greater than 50 mg. Bicalutamide 150 mg is NOT to be administered.

If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, bicalutamide should be interrupted and prompt investigation initiated. If Interstitial Lung Disease is confirmed, bicalutamide should be discontinued and the patient treated appropriately.

Special Populations

Pregnant and Nursing Women: Bicalutamide is contraindicated in females. Bicalutamide may cause fetal harm when administered to pregnant women. The male offspring of rats (but not rabbits) receiving doses of 10 mg/kg/day and above, were observed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits (receiving doses up to 200 mg/kg/day) or rats (receiving doses up to 250 mg/kg/day).

Pediatric: The safety and effectiveness of bicalutamide (non-steroidal antiandrogen) in children has not been established.

Monitoring and Laboratory Tests

Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring patients' response.

Anemia has been observed in patients treated with bicalutamide. Hemoglobin levels should be monitored.

Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving bicalutamide should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Since transaminase abnormalities and jaundice, rarely severe, have been reported with the use of bicalutamide, periodic liver function tests should be considered. If clinically indicated, discontinuation of therapy should be considered. Abnormalities are usually reversible upon discontinuation.

Since bicalutamide may elevate plasma testosterone and estradiol levels, fluid retention could occur. Accordingly, bicalutamide should be used with caution in those patients with cardiac disease.

A reduction in glucose tolerance has been observed in males receiving bicalutamide in combination with LHRH analogues. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose and/or glycated hemoglobin (HbAlc) in patients receiving bicalutamide in combination with LHRH analogues, especially diabetic patients (See WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Bicalutamide in Metastatic Patients

In patients with advanced prostate cancer, treated in the multicentre, double-blind controlled clinical trial comparing bicalutamide 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the most frequent adverse experiences included: hot flushes (53%), asthenia (22%), constipation (22%), nausea (14%), peripheral edema (13%), anemia (13%), haematuria (12%), abdominal pain (11%), dizziness (10%), gynecomastia (9%), rash (9%), chest pain (8%), erectile dysfunction (7%), flatulence (7%), dyspepsia (7%), decreased appetite (6%), breast tenderness (6%), weight increase(5%), cardiac failure (4%), depression (4%), dry skin (4%), alopecia (4%), pruritus (3%), somnolence (3%), myocardial infarction (3%), decreased libido (2%), hirsutism (2%), and hypersensitivity reactions (1%) including angioedema and urticaria.

Adverse event reports of abnormal liver function test results occurred in 7% of patients. These changes were frequently transient and rarely severe, resolving or improving with continued therapy or following cessation of therapy.

Hepatic failure and interstitial lung disease (see WARNINGS AND PRECAUTIONS) have been observed in post-marketed data and fatal outcomes have been reported for both.

Bicalutamide, in general has been well tolerated with few withdrawals due to adverse events. The most common adverse events leading to withdrawal of study medication were abnormal liver function tests (1.5%), hot flushes (1.0%), and nausea and vomiting (0.7%).

After a 160 week follow-up, there were 213/401 deaths in the Bicalutamide -LHRH arm and 235/407 deaths in the flutamide-LHRH arm of the trial. There were 30 vs. 18 deaths due to

adverse events in the two arms respectively and in both arms, the most common causes of death due to adverse events were attributed to the cardiovascular system (see 'Cardiovascular' under the 'Clinical Trial Adverse Drug Reactions' sub-section below).

Myocardial infarction and cardiac failure were observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when bicalutamide was used in combination with LHRH agonists. Fatal outcomes of myocardial infarction have been reported.

Clinical Trial Adverse Drug Reactions

The following adverse experiences were reported within the same clinical trial with an incidence of ≥5%, regardless of causality.

Table 1 Incidence of Adverse Events (≥ 5% in Either Treatment Group) Regardless of Causality

Adverse Event	Treatment Group Number of Patients (%)			
	Bicalutamide Plus LHRH Analogue (n=401)		Flutamide Plus LHRH Analogue (n=407)	
Hot Flushes	211	(53)	217	(53)
Pain (General)	142	(35)	127	(31)
Back Pain	102	(25)	105	(26)
Asthenia	89	(22)	87	(21)
Constipation	87	(22)	69	(17)
Pelvic Pain	85	(21)	70	(17)
Infection	71	(18)	57	(14)
Nausea	56	(14)	54	(13)
Peripheral Edema	53	(13)	42	(10)
Anemia[a]	51	(13)	60	(15)
Dyspnea	51	(13)	32	(8)
Diarrhea	49	(12)	107	(26)
Nocturia	49	(12)	55	(14)
Hematuria	48	(12)	26	(6)
Abdominal Pain	46	(11)	46	(11)
Dizziness	41	(10)	35	(9)
Bone Pain	37	(9)	43	(11)
Gynecomastia	36	(9)	30	(8)
Rash	35	(9)	30	(7)
Urinary Tract Infection	35	(9)	36	(9)
Chest Pain	34	(8)	34	(8)
Hypertension	34	(8)	29	(7)
Cough Increased	33	(8)	24	(6)
Pharyngitis	32	(8)	23	(6)
Paresthesia	31	(8)	40	(10)
Increased Liver Enzyme Test[b]	30	(7)	46	(11)

Adverse Event	Treatment Group Number of Patients (%)			
	Bicalutamide Plus LHRH Analogue (n=401)		Flutamide Plus LHRH Analogue (n=407)	
Weight Loss	30	(7)	39	(10)
Headache	29	(7)	27	(7)
Flu Syndrome	28	(7)	20	(5)
Myasthenia	27	(7)	19	(5)
Insomnia	27	(7)	39	(10)
Erectile Dysfunction	27	(7)	35	(9)
Flatulence	26	(7)	22	(5)
Hyperglycemia	26	(7)	27	(7)
Dyspepsia	26	(7)	23	(6)
Decreased Appetite	25	(6)	29	(7)
Sweating	25	(6)	20	(5)
Bronchitis	24	(6)	11	(3)
Breast Pain (tenderness)	23	(6)	15	(4)
Urinary Frequency	23	(6)	29	(7)
Alkaline Phosphatase Increased	22	(5)	24	(6)
Weight Increased	22	(5)	18	(4)
Arthritis	21	(5)	29	(7)
Anxiety	20	(5)	9	(2)
Urinary Retention	20	(5)	14	(3)
Urinary Impaired	19	(5)	15	(4)
Pneumonia	18	(4)	19	(5)
Pathological Fracture	17	(4)	32	(8)
Depression	16	(4)	33	(8)
Vomiting	16	(4)	28	(7)
Rhinitis	15	(4)	22	(5)
Urinary Incontinence	15	(4)	32	(8)

[a]Anemia includes hypochromic anemia and iron deficiency anemia.
[b]Abnormal liver function tests reported as adverse events.

In addition, the following adverse experiences were reported by investigators within the same clinical trial (as possible adverse drug reactions in the opinion of investigating clinicians) with a frequency of less than 5%, during treatment with bicalutamide 50 mg plus an LHRH analogue. These experiences are not necessarily considered as causally related to drug treatment.

Cardiovascular: In the pivotal trial of 813 patients comparing bicalutamide 50 mg once daily with Flutamide 250 mg three times a day, each in combination with an LHRH analogue, an imbalance of deaths related to cardiovascular adverse events was noted Bicalutamide-LHRH therapy: 18 deaths; Flutamide-LHRH therapy: 9 deaths) however, there is difficulty in interpreting this imbalance as the exposure was longer on the Bicalutamide-LHRH arm by a mean of 13 weeks. Other cardiovascular-related experiences reported include angina pectoris, congestive

	heart failure, myocardial infarction, heart arrest, coronary artery disorder, syncope, atrial fibrillation, cerebrovascular accident, deep thrombophlebitis, arrhythmia, bradycardia, cerebral ischemia, hemorrhage.
Central Nervous System:	hypertonia, confusion, somnolence, decreased libido, neuropathy, nervousness
Endocrine System:	diabetes mellitus
Gastrointestinal:	melena, rectal hemorrhage, dry mouth, dysphagia, gastrointestinal disorder, periodontal abscess, gastrointestinal carcinoma, rectal disorder, intestinal obstruction, gastritis
Hematological:	ecchymosis, thrombocytopenia
Immune System Disorders:	hypersensitivity, angioedema and urticaria.
Metabolic & Nutritional:	edema, BUN increased, creatinine increased, dehydration, gout, hypercholesteremia, hypoglycemia, hypercalcemia
Musculoskeletal	leg cramps, bone disorders, myalgia
Respiratory System:	lung disorder, asthma, epistaxis, sinusitis, pleural effusion, voice alteration
Skin & Appendages:	dry skin, alopecia, pruritus, herpes zoster, skin carcinoma, skin disorder, skin hypertrophy, hirsutism, skin ulcer
Special Senses:	cataract, abnormal vision, conjunctivitis
Urogenital:	dysuria, urinary urgency, hydronephrosis, urinary tract disorder, bladder stenosis, kidney calculus, prostatic disorder, balanitis
Whole Body:	neoplasm, neck pain, fever, chills, sepsis, hernia, cyst, injection site reaction, allergic reaction, neck rigidity, face edema

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, creatinine and decreased haemoglobin and white cell count have been reported in both bicalutamide-LHRH analogue treated and flutamide-LHRH analogue treated patients. Increased liver enzyme tests and decreases in haemoglobin were reported less frequently with Bicalutamide-LHRH analogue therapy. Other changes were reported with similar incidence in both treatment groups.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of bicalutamide:

Cardiovascular:	Myocardial infarction (fatal outcomes have been reported, cardiac failure, sudden cardiac death)
Hepato-biliary disorders:	Hepatic failure (fatal outcomes have been reported)
Hematologic:	Anaemia
Respiratory:	Interstitial lung disease (fatal outcomes have been reported)

DRUG INTERACTIONS

Drug-Drug Interactions

Clinical studies with bicalutamide have not demonstrated any drug/drug interactions with LHRH analogues.

In vitro studies have shown that the R-enantiomer is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Although *in vitro* studies have suggested the potential for bicalutamide to inhibit cytochrome 3A4, a number of clinical studies show the magnitude of any inhibition is unlikely to be of clinical significance for the majority of substances which are metabolised by cytochrome P450. Nevertheless, such an increase in AUC could be of clinical relevance for drugs with a narrow therapeutic index (e.g. cyclosporin).

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is recommended that if bicalutamide is started in patients who are already receiving coumarin anticoagulants prothrombin time should be closely monitored and adjustment of the anticoagulant dose may be necessary.

Bicalutamide is indicated for use in combination with either an LHRH analogue or surgical castration. Since combined androgen blockade prolongs the QTc interval, the combination use of bicalutamide with an LHRH analogue, and medicinal products known to prolong the QTc interval or able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor analogues (e.g. salbutamol).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
BICALUTAMIDE 50 mg in metastatic disease: The recommended dose for BICALUTAMIDE (bicalutamide) therapy in combination with an LHRH analogue or surgical castration is one 50 mg tablet once daily with or without food. BICALUTAMIDE treatment should be started at the same time as treatment with an LHRH analogue or after surgical castration.

Dosing Considerations in Special Populations
Renal or Hepatic Impairment: No dosage adjustment is necessary for patients with renal or mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

A single dose of bicalutamide that results in symptoms of an overdose considered to be life-threatening has not been established. In animal studies, bicalutamide demonstrated a low potential acute toxicity. The LD_{50} in mice and rats was greater than 2000 mg/kg. Long-term clinical trials have been conducted with doses up to 200 mg of bicalutamide daily and these doses have been well tolerated.

There is no specific antidote; treatment of an overdose should be symptomatic. In the management of an overdose with bicalutamide, vomiting may be induced if the patient is alert. It should be remembered that in this patient population multiple drugs may have been taken. Dialysis is not likely to be helpful since bicalutamide is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics
Bicalutamide is a non-steroidal antiandrogen, devoid of other endocrine activity. Bicalutamide competitively inhibits the action of androgens by binding to cytosol androgen receptors in target tissue. This inhibition results in regression of prostatic tumours. Bicalutamide is a

racemate and the (R)-enantiomer is primarily responsible for the antiandrogenic activity of bicalutamide.

Pharmacokinetics

The absorption, distribution, metabolism and excretion of bicalutamide have been investigated after administration of a single 50 mg oral dose to volunteers. The results indicated that the dose was extensively absorbed and was excreted almost equally in urine (36%) and faeces (43%) over a 9 day collection period. There is no evidence of any clinically significant effect of food on bioavailability. Steady state plasma concentrations of the (R)-enantiomer of approximately 9 μg/ml are observed during daily administration of 50 mg doses of bicalutamide. At steady state, the active (R)-enantiomer accounts for 99% of the circulating plasma bicalutamide concentration. Bicalutamide is highly protein bound (racemate 96%, (R)-enantiomer 99.6%). On daily administration, the (R)-enantiomer accumulates about 10- fold in plasma, consistent with an elimination half-life of approximately one week. The (S)-enantiomer is very rapidly cleared relative to the (R)-enantiomer. Bicalutamide is extensively metabolized via both oxidation and glucuronidation with approximately equal renal and biliary elimination of the metabolites.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of the (R)-enantiomer are unaffected by age.

Geriatrics: The pharmacokinetics of the (R)-enantiomer are unaffected by age.

Hepatic Insufficiency: The pharmacokinetics of the (R)-enantiomer are unaffected by mild to moderate hepatic impairment. Patients with severe hepatic impairment eliminate the (R)-enantiomer from plasma more slowly.

Renal Insufficiency: The pharmacokinetics of the (R)-enantiomer are unaffected by renal impairment.

STORAGE AND STABILITY

Store between 15°C and 30°C.
Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets

50 mg: Each round, white, coated tablet, debossed with "BIC" over "50" on one side and plain on the other side contains 50 mg of bicalutamide and the following nonmedicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethelyne glycol, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, triethyl citrate. Available in bottles of 100 and 500 tablets and blister packs of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

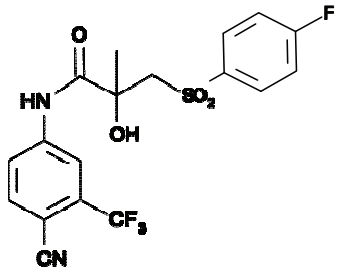
Proper Name: Bicalutamide

Chemical Name: (RS)-4'-Cyano-α'-α'α'- trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-m-toluidide (IUPAC)

Molecular Formula: $C_{18}H_{14}N_2O_4F_4S$

Molecular Mass: 430.4 g/mol

Structural Formula:



Physiochemical Properties: Bicalutamide is a fine white to off white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingl yoluble in methanol, and soluble in acetone and tetrahydrofuran. The pKa is approximately 12.

BICALUTAMIDE is a racemate with its antiandrogen activity being predominately exhibited by the (R)-enantiomer of bicalutamide.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study of BICALUTAMIDE tablets was performed versus Casodex® using healthy adult volunteers. Pharmacokinetic and bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILOTY DATA

Bicalutamide 1 X 50 mg From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test BICALUTAMIDE**	**Reference Casodex®‡**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng.h/mL)	49169.01 49689.0 (14.9)	46659.35 48257.5 (14.71)	105.38	97.15-114.31
C_{max} (ng/mL)	808.13 815.9 (14.11)	779.06 786.8 (13.78)	103.73	96.80-111.16
T_{max}* (h)	26.6 (46.39)	31.7 (31.51)	--	--

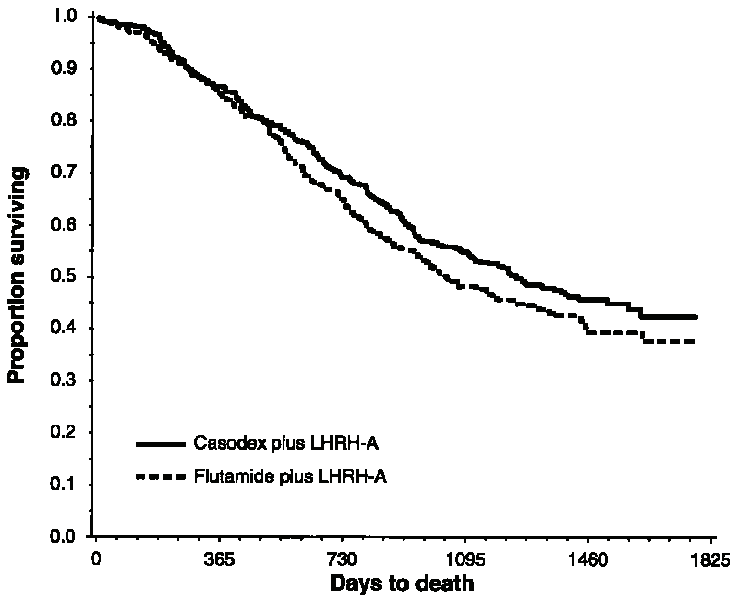
*T_{max} is presented as the mean (CV%)
‡Casodex® is manufactured by AstraZeneca Canada Inc., and was purchased in Canada.
Note: Due to the reported long terminal half-life of Bicalutamide, the terminal elimination constant, K_{el}, could not be reliable estimated in this study and therefore, parameters derived from K_{el}, such as $T_{1/2el}$ and AUC_I, are not provided in the summary table.

Study demographics and trial design
Time to treatment failure was the primary endpoint of a large, double-blinded, multicentre, non-inferiority clinical trial. Eight-hundred thirteen (813) patients with previously untreated advanced prostate cancer were randomized to receive bicalutamide 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with luteinizing hormone-releasing hormone (LHRH) analogues (either goserelin acetate implant or leuprolide acetate depot).

Study results
Approval was based on a median follow-up of 49 weeks which showed Bicalutamide-LHRH analogue therapy was associated with a statistically significant (p=0.005) improvement in time to treatment failure. With a longer follow-up (median 95 weeks), improvement in time to treatment failure was no longer statistically significant (p=0.10).

In a survival analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with Bicalutamide-LHRH analogue therapy and 235 (57.5%) patients treated with Flutamide-LHRH analogue therapy had died. There was no significant difference in survival between treatment groups (see Figure 1). The hazard ratio for survival was 0.87 (95% confidence interval 0.72 to 1.05, p=0.15).

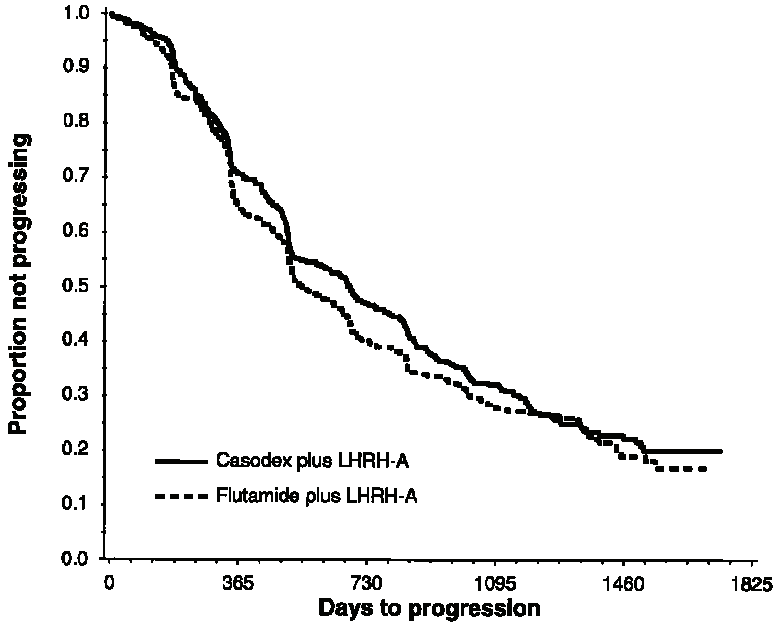
Figure 1 The Kaplan-Meier probability of survival for both antiandrogen treatment groups.



There was no significant difference in time to objective tumour progression between treatment groups (see Figure 2). Objective tumour progression was defined as the appearance of any bone metastases or the worsening of any existing bone metastases on bone scan attributable to

metastatic disease, or an increase by 25% or more of any existing measurable extraskeletal metastases. The hazard ratio for time to progression of bicalutamide plus LHRH analogue to that of flutamide plus LHRH analogue was 0.93 (95% confidence interval, 0.79 to 1.10, p=0.41).

Figure 2 **Kaplan-Meier curve for time to progression for both antiandrogen treatment groups.**



Quality of life was assessed using a self-administered patient questionnaire on pain, bed disability, activity limitation, physical capacity, social functioning, emotional well-being, vitality, overall health, general symptoms, and treatment-related symptoms. At a median follow-up of 95 weeks, no significant differences were noted between the two treatment groups.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics:

In vitro

Bicalutamide binds to rat, dog and human prostate and rat pituitary androgen receptors. In radioligand displacement assays, graded doses of bicalutamide inhibit the binding of the synthetic androgen [^{3}H] -R-1881. Using the rat prostate androgen receptor, the displacement curves for bicalutamide, the antiandrogen hydroxyflutamide, R-1881 and the natural ligand, 5α-dihydrotestosterone are parallel.

Bicalutamide binds around fifty times less effectively than 5α-dihydrotestosterone and around 100 times less effectively than R-1881 to the rat androgen receptor but has an affinity around 4-fold higher for the prostate and 10 times higher for the pituitary androgen receptor than hydroxyflutamide. The relative affinities of bicalutamide for dog and human prostate androgen receptors are similar to those for the rat and are again higher than for hydroxyflutamide. Bicalutamide has no effect on prostate steroid 5α-reductase and has negligible affinity for the sex hormone-binding globulin and no affinity for corticosteroid-binding globulin.

In vivo

Rat: In the rat, bicalutamide and the (R)-enantiomer are at least 1000 times more potent as antiandrogens than the (S)-enantiomer which had very low potency. In immature castrated rats, 0.5 mg/kg oral bicalutamide prevents stimulation of the growth of the seminal vesicles and ventral prostate gland in response to daily subcutaneous injections of testosterone propionate (200 µg/kg). In intact mature rats, several studies show that bicalutamide causes a dose-related reduction in accessory sex organ weights. In these studies bicalutamide had only a minimal effect on serum luteinizing hormone and testosterone.

Dog: Studies show that bicalutamide is an effective antiandrogen at the dog prostate but does not elevate serum testosterone concentrations. The ED_{50} value for inducing prostate atrophy in the dog following daily oral treatment for 6 weeks is about 0.1 mg/kg. At all doses tested up to 100 mg/kg, bicalutamide has no effect on serum testosterone concentrations.

Monkey: Longitudinal studies in monkeys, where prostate and seminal vesicle sizes were followed by magnetic resonance imaging, show bicalutamide to be a highly potent (1-5 mg/kg) antiandrogen with negligible effect on serum testosterone, although there was wide intra- and inter-animal variability.

Pharmacokinetics:

Bicalutamide displays enantioselective pharmacokinetics in rats, dogs and man with the (R)-enantiomer being slowly eliminated, particularly in the dog and man, and consequently accumulating on daily administration. Steady state ratios (R)-enantiomer to (S)-enantiomer are highest in man (~100:1), lower in the rat (~14:1) and even lower in the dog (~3:1).

TOXICOLOGY

Acute Toxicity

In animal studies, bicalutamide demonstrated a low potential acute toxicity. The LD_{50} in mice, rats and dogs was greater than 2000 mg/kg. The LD_{50} in rabbits was greater than 200 mg/kg.

Long-Term Toxicity

Multiple dose studies include one, six and twelve month studies in the rat and dog (see following table).

Table 2 Long-Term Toxicity

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Rat Winstar	1 month	28-40 M* + 28-40 F*	Oral	0 25 100 500	Minor, reversible drug related increases (<10%) in plasma total protein & albumin in Groups III and IV. Small prostate and seminal vesicles at all doses and reversible, drug related increase in liver weight (21% and 35% for Groups III and IV males, 36%, 55% and 90% for Groups II-IV females) and adrenal weights (24% and 50% for Group III and IV males, 16% and 27% for Group III and IV females). Microscopic changes were consistent with anti-androgen activity (e.g. atrophy of ventral prostate & seminal vesicles, Leydig cell hyperplasia). There were changes consistent with enzyme induction in the liver in bicalutamide-dosed groups and a minimal to mild increases in cortical single cell necrosis in adrenal glands in bicalutamide -dosed groups and a minimal to mild hypertrophy of follicular epithelium and reduced colloid, in the thyroid gland from dosed groups. There was a dose dependant increase in basophilia and RNA content of hepatocyte cytoplasm in all bicalutamide -dosed groups and an increase in smooth ER in some Group IV animals.
Rat Winstar	6 months	30-57 M* + 30-57 F*	Oral	0 10 50 250	There were small reductions in body weight and a reduction in alkaline phosphatase in dosed males. A small, reversible increase in plasma protein and albumin, a decrease in packed cell volume and haemoglobin was seen in all bicalutamide -dosed groups. Expected reversible size reduction in prostate and seminal vesicles (all dosed) and testes (Groups III & IV); some Group IV males had enlarged testes. Increased adrenal gland weight in all groups - increased weight of liver, kidneys, heart (females only) and brain, not accompanied by important histological change. Histopathological changes were seen in the prostate and seminal vesicles (atrophy), testes (atrophy of seminiferous tubules and Leydig cell hyperplasia), ovaries (granulosa-thecal cell hyperplasia), adrenals (cortical hypertrophy to cortical vacuolation), pituitary glands in males (castration cells) and thyroid gland (epithelial cell hypertrophy). Many of

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
					these changes were reduced or reversed in the drug withdrawal period - the adrenal cortical vacuolation and castration cells in pituitary were largely unchanged.
Rat Wistar	12 month	33-45 M* + 33-45 F*	Oral in diet	0 5 15 75	Increased incidence of small/flaccid testes in Groups III & IV, small reduction in male body weight, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase and a small reversible reduction in haemoglobin & related indices in Group IV females. There was a small increase in plasma total protein. There was an increase in liver weight in Groups III & IV accompanied by hepatocyte hypertrophy and basophilia, related to MFO induction. Other histological changes were limited to the reproductive and some endocrine organs - increased adrenal weight, hypertrophy of the thyroid follicular epithelium, follicular epithelium hyperplasia and colloid basophilia, testicular tubular atrophy (Group III & IV), atrophy of prostate and seminal vesicles - except for testicular atrophy, changes reversed or showed signs of recovery following withdrawal. There was an increase in tumours in three hormonesensitive organs, benign testicular Leydig cell tumours (all dosed groups), thyroid follicular adenomas (Group IV) and uterin carcinomas (Group IV) at the end of the withdrawal period.
Dog Beagle	6 weeks	2 M + 2 F	Oral	0 25 75 150	There was a reduction in the weight of the testes, epididymides & prostate gland in dosed groups and atrophy of the seminiferous tubules and diffuse Leydig cell hyperplasia; the epididymides showed minimal/mild microcystic degeneration and spermatozoa were absent. Adrenal glands of dogs given bicalutamide were increased in weight; there was cytoplasmic vacuolation of the cortex (changes related to bicalutamide administration); there were no bicalutamide-related changes in the female reproductive tract. Significant increases in heart rate (28-39 BPM) were seen in all groups by week 5. The P-R interval was reduced in all groups (21-26 msec, week 5); there were no important differences in blood pressure and no changes were seen on the electrocardiogram for any dog. There was an increase in plasma cholesterol (1.5 times control)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
					at all time points for Groups III & IV; there was a mild phenobarbital-like induction of cytochrome P450.
Dog Beagle	6 months	5-8 M* + 5-8 F*	Oral	0 2.5 10 100	Two males (Group III & IV) were killed because of infection, 1 Group IV female with an infection during week 20 recovered. Body weight (8%) and food intake were reduced in the first 6 weeks in Group IV; this group gained weight in the withdrawal period. A dose related reduction in P-R interval was seen; the changes (Group IV) reversed 4 weeks after drug withdrawal; there were no histological findings in the heart associated with these changes. There was a reduction in weight & diffuse atrophy of the prostate gland (all doses), Leydig cell hyperplasia, seminiferous tubule atrophy, arrested spermatogenesis of the testes, ductal atrophy of the epididymides, endometrial gland reduction of the uterus, increased keratinisation of the cervix and vagina, atrophy of the mammary gland and increased weight, cortical vacuolation and cortical hypertrophy of the adrenal glands; effects associated with anti-androgenic activity. Following 16 weeks drug withdrawal Group IV animals showed no evidence of atrophy of the prostate; other changes in the male and female reproductive tract were absent or less marked. Cortical vacuolation of the adrenal gland was still present.
Dog Beagle	12 months	5-8 M* + 5-8 F*	Oral	0 1 2.5 50	There was a decrease in mean P-R interval in Group III & IV (7-16% & 16-22% respectively). There was a higher liver weight and small increases in alkaline phosphatase in Group IV because of enzyme-induction. Increases in plasma glucose, urea, cholesterol and in alanine aminotransferase in Group IV, were a result of antiandrogenic activity. There was decrease in weight and atrophy of the prostate gland, changes in the testes (Leydig cell hyperplasia, exfoliated seminiferous epithelial cells, maturation arrest) and epididymides (stromal hyperplasia, ductal atrophy, sperm reduction) at all doses and mammary glands (reduced acinar development) in Groups III & IV; these were anti-androgen related effects. Following 6 months withdrawal there was no compoundrelated

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
					changes in the male reproductive tract; reduced acinar development was present in all high dose females. There was increased weight and cortical vacuolation of the adrenal glands (all dosed groups) and cortical hypertrophy and hyperplasia (Groups III & IV); on withdrawal both adrenal weight and vacuolation showed evidence of reversibility but cortical hyperplasia was still evident.

*Reflects group related extra animals (eg. for pharmacokinetic, coagulation, haematology and drug withdrawal).

Carcinogenicity
Two-year oral oncogenicity studies in both male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide have been completed. A variety of tumour target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely testicular benign interstitial (Leydig) cell tumours in rats at all dose levels (the steady state plasma concentration with the 5 mg/kg/day dose is comparable to a human oral 50 mg/day dose) and uterine adenocarcinoma in rats at 75 mg/kg/day (3 times greater than the human plasma concentration, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient). There is no evidence of Leydig cell hyperplasia in patients treated in combination with LHRH analogues. Uterine tumours are not relevant to the indicated patient population.

A small increase in incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (plasma concentration 4 times greater than the human concentration) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg and above 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 following bicalutamide administration in man. There were no tumourigenic effects suggestive of genotoxic carcinogenesis.

Mutagenicity
A comprehensive battery of both *in vitro* and *in vivo* genotoxicity tests has demonstrated that bicalutamide does not have genotoxic activity.

Reproduction & Teratology
Reproduction and teratology studies have been conducted in the rat and rabbit (see following table).

Table 3 Reproduction and Teratology

Species	Duration	No. of Animals/Dose	Route	Dose mg/kg/day	Type of Study	Effects
Rat Wistar	11 weeks	25 M + 150 F	Oral	0 0.25 5 250	Male Fertility	In male rats dosed at 250 mg/kg/day, the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an eleven week period of dosing.
Rat Wistar	2 wks before mating through pregnancy & lactation*	6 M + 6 F	Oral	0 10 250	Female Fertility	No effects on dosed females (10 and 250 mg/kg/day) or their female offspring were observed. As an antiandrogen, there was feminization of the male offspring of all dosed females leading to hypospadias. Affected male offspring were also impotent.
Rat Wistar	days 6-15	20 pregnant per group**	Oral	0 1 10 50 250	Teratology	The offspring of rats dosed at 0, 1, 10, 50 and 250 mg/kg/day and rabbits dosed at 0, 10, 50 and 200 mg/kg/day did not show evidence of any developmental or teratogenic effect. The only developmental abnormality seen was a predictable reduction of anogenital distance due to the androgenic properties of the drug in only male fetuses at doses of 10, 50 and 250 mg/kg/day; no effect was seen at 1 mg/kg/day. Feminization of the male offspring of all females dosed at 10 and 50 mg/kg/day was reported in a fertility and reproductive study in rats.
Rabbit Dutch Belled	days 6-18	20 pregnant per group***	Oral	0 10 50 200	Teratology	

* Up to twelve weeks
** An extra 4 females were added for pharmacokinetic samples
*** An extra 6 females were added for pharmacokinetic sample

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PART III: CONSUMER INFORMATION

Pr BICALUTAMIDE
bicalutamide tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
BICALUTAMIDE is used in the treatment of advanced prostate cancer in combination with other drugs (LHRH analogues) which reduce the levels of androgens in the body or surgery.

What it does:
Androgens are male sex hormones within the body which can cause tumour growth within the prostate. BICALUTAMIDE belongs to a group of medicines called non-steroidal antiandrogens. This means that BICALUTAMIDE interferes with some of the actions of androgens to prevent the tumour from growing.

What are the Stages of Prostate Cancer:
- Localized disease- the early stages of disease when prostate cancer is confined to the prostate gland
- Locally advanced disease- the disease progresses and the cancer spreads to other tissues within the pelvis
- Advanced or metastatic disease- the disease progresses to other parts of the body

The PSA (Prostate Specific Antigen) test is a simple blood test for a protein produced by the prostate (PSA). This test has helped in the detection of prostate cancer resulting in an increase in the number of men whose prostate cancer is detected at an early stage.

What are the Treatment Options for Localized Prostate Cancer:
The optimal treatment for a given individual will depend on the specific circumstances of his case. For localized disease, patients are usually offered one of the following:
- Surgery to remove the prostate
- Targeted radiotherapy to kill the cancer cells in the prostate
- No treatment initially (watchful waiting) whereby the patient is monitored until there are signs of progression before treatment is started.

When it should not be used:
- Do not take BICALUTAMIDE if you have early phase (localized) prostate cancer requiring watchful waiting.
- Do not take BICALUTAMIDE if you are allergic to bicalutamide or any of the nonmedicinal ingredients in BICALUTAMIDE.
- BICALUTAMIDE must not be taken by women, including pregnant women or mothers who are breast feeding their babies.
- BICALUTAMIDE must not be given to children.

What the medicinal ingredient is:
Bicalutamide

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, polydextrose, polyethelyne glycol, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, triethyl citrate

What dosage forms it comes in:
Tablets: 50 mg

WARNINGS AND PRECAUTIONSu

- **BICALUTAMIDE should only be prescribed by a doctor experienced with the treatment of prostate cancer.**
- **BICALUTAMIDE 150 mg/day dose should not be used.**
- **BICALUTAMIDE may rarely be associated with liver failure; some cases have been fatal.**
- **BICALUTAMIDE may be associated with uncommon cases of interstitial lung disease; some cases have been fatal.**

BEFORE you use BICALUTAMIDE talk to your doctor or pharmacist if:
- You have liver disease.
- You have lung disease.
- You have low bone mineral density (BMD)
- You have low red blood cell count (anemia).

- You have heart disease, or have a heart condition called "long QT syndrome" or family history of this heart condition

If you go into hospital let the medical staff know you are taking BICALUTAMIDE.

BICALUTAMIDE may make you feel sleepy. Do not drive or use machines until you know how the drug affects you.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed.

- In particular please inform your doctor if you are taking oral anti-coagulants (to prevent blood clots)
- If you are taking any medicines that may increase the risk of having an abnormal heart rhythm.

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions about when and how to take your tablets. Ask your doctor or pharmacist if you are not sure.

- The usual adult dose is 50 mg daily.
- Swallow the tablet(s) whole with a drink of water
- Try to take your dose at the same time each day.

During the first few months of use, you may be monitored by your physician for signs of changes in your liver function. In approximately 2.0% of patients, such changes may lead to withdrawal of therapy.

If you experience a rise in PSA while taking BICALUTAMIDE, your physician may discontinue BICALUTAMIDE for several weeks in order to monitor your condition off treatment.

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:

You should take BICALUTAMIDE as prescribed. However, if you miss a dose, do not take an extra dose; just resume your usual schedule.

SIDE EFFETS AND WHAT TO DO ABOUT THEM

Like all medicines, BICALUTAMIDE 50 mg can have side effects.

Side effects that are very common (more than 10 in every 100 patients are likely to have them):

- dizziness
- nausea
- hot flushes
- feeling weak
- decreased red blood cell count (anemia)
- puffiness/swelling
- constipation

Side effects that are common (1 to 10 in every 100 patients are likely to have them):

- loss of appetite
- reduced sex drive
- depression
- sleepiness
- indigestion
- flatulence
- loss of hair or hair re-growth
- rash
- itching
- dry skin
- impotence
- chest pain
- tender or enlarged breast tissue
- weight gain
- heart failure
- heart attack

Occasionally BICALUTAMIDE may be associated with changes in your blood which may require your doctor to do certain blood tests.

SERIOUS SIDE EFFETS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
	Only if severe	**In all cases**	
Very Common (more than 10 in every 100 patients are likely to have them)			
Blood in urine		✓	
Abdominal pain		✓	
Common (1 to 10 in every 100 patients are likely to have them)			
Yellow skin and eyes (jaundice). These may be symptoms of liver damage.		✓	
Heart failure (reduced heart function)		✓	
Heart attack		✓	
Uncommon (1 to 10 in every 1000 patients are likely to have them)			
Serious breathlessness, or sudden worsening of breathlessness, possibly with a cough or fever. Some patients taking bicalutamide 50 mg get an inflammation of the lungs called interstitial lung disease.		✓	
Severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing		✓	

Tell your doctor or pharmacist if you think you have any of these or any other problems with your tablets.

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

HOW TO STORE IT

- Keep your tablets in the container they came in.
- Do not take your tablets after the expiry date on the container. Dispose of them in an appropriate way.
- Keep your tablets in a safe place where children cannot see or reach them. Your tablets could harm them.
- Keep your tablets between 15°C and 30°C. Protect from light.

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 0701E
  Ottawa, Ontario
  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, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Sorres Pharma Inc. at 1-888-550-6060.

This leaflet was prepared by:

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