PRODUCT MONOGRAPH

[Pr]AVA-BICALUTAMIDE

(bicalutamide)

50 mg Tablets

Non-Steroidal Antiandrogen

Avanstra Inc.
10761 – 25th NE
Suite 110, Building "B"
Calgary, Alberta
T2C 3C2
Canada

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50mg Tablets

Non-Steroidal Antiandrogen

CLINICAL PHARMACOLOGY

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

Pharmacokinetics and Metabolism

The absorption, distribution, metabolism and excretion of bicalutamide has 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. The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. Patients with severe hepatic impairment eliminate the (R)-enantiomer from plasma more slowly. Bicalutamide is extensively metabolized via both oxidation and glucuronidation with approximately equal renal and biliary elimination of the metabolites.

Clinical Experience

In a large multicentre, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive 50 mg of bicalutamide 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). At a median follow-up of 49 weeks, 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 ($p = 0.10$). At the same timepoint, 130 (32%) patients treated with bicalutamide-LHRH analogue therapy and 145 (35%) patients treated with flutamide-LHRH analogue therapy had died. Subjective responses, (including scores for pain, analgesic use and Eastern Oncology Cooperative Group (ECOG) performance status) assessed in patients with symptoms at entry were seen in 95 (52%) patients treated with bicalutamide and in 88 (54%) patients treated with flutamide, each in combination therapy with LHRH analogues. This small

difference was not statistically significant between 50 mg of bicalutamide combination therapy and flutamide combination therapy.

A comparative, two-way, single-dose bioavailability study was performed under fasting conditions on AVA-BICALUTAMIDE (bicalutamide) 50 mg tablets and CASODEX® 50 mg tablets. The pharmacokinetic data calculated for the two bicalutamide formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA
AVA-BICALUTAMIDE Tablets
(1 x 50 mg)
From measured data
Geometric Mean
Arithmetic Mean (CV%)

Parameters***	AVA-Bicalutamide	Casodex®**	Ratio of Geometric Means (%)	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	47283.26 48129.42 (18.5)	50416.31 51089.68 (16.9)	93.79	85.88-102.42
C_{max} (ng/mL)	818.62 834.92 (19.7)	876.76 890.41 (18.3)	93.37	84.04-102.52
T_{max} * (h)	33.00 (9.00-72.00)	30.00 (3.00-48.00)	-	-

*For T_{max}, the median (range) is presented
**Casodex® 50 mg Tablets manufactured by AstraZeneca Canada Inc.; purchased in Canada
***Due to the nature of the study design, the meaningful AUC_I and $T_{1/2}$ parameters could not be calculated and thus are not provided

INDICATIONS AND CLINICAL USE

AVA-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.

CONTRAINDICATIONS

AVA-BICALUTAMIDE (bicalutamide) is contraindicated in the following:

- Patients with localized prostate cancer otherwise undergoing watchful waiting. (See WARNINGS)
- Patients with hypersensitivity to the drug or any of its components.
- Women: The safety and effectiveness of AVA-BICALUTAMIDE in women has not been studied.
- Children: The safety and effectiveness of AVA-BICALUTAMIDE in children has not been studied.

WARNINGS

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. In the absence of factors suggesting high risk of disease progression, it is recommended that clinicians do not administer AVA-BICALUTAMIDE 150 mg in patients with localized prostate cancer. 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 50mg per day for the treatment of metastatic prostate cancer are not affected by this new information.

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.

PRECAUTIONS

Localized Prostate Cancer Patients

It is recommended that AVA-BICALUTAMIDE 150 mg is NOT administered to patients with localized disease who would otherwise undergo watchful waiting.

Pediatric Use

The safety and effectiveness of AVA-BICALUTAMIDE (non-steroidal antiandrogen) in children has not been established.

Pregnancy and Lactation

AVA-BICALUTAMIDE is contraindicated in females. AVA-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).

Patients with Hepatic Impairment

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

Severe hepatic changes have been observed rarely with bicalutamide. AVA-BICALUTAMIDE therapy should be discontinued if changes are severe.

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.

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 metabilised 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 AVA-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.

Laboratory Tests

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

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 AVA-BICALUTAMIDE may elevate plasma testosterone and oestradiol levels, fluid retention could occur. Accordingly, AVA-BICALUTAMIDE should be used with caution in those patients with cardiac disease.

ADVERSE REACTIONS

Bicalutamide in Metastatic Patients

Bicalutamide, in general has been well tolerated with few withdrawals due to adverse events.

Frequency of Adverse Reactions

Frequency	System Organ Class	Event
Very Common (≥10%)	Reproductive system and breast disorder	Breast tenderness[1]
		Gynaecomastla[1]
	General disorders	Hot flushes[1]
Common (≥ 1% and < 10%)	Gastrointestinal disorders	Diarrhoea
		Nausea
	Hepato-biliary disorders	Hepatic changes (elevated levels of transaminases, jaundice)[2]
	General disorders	Asthenia
		Pruritis
Uncommon (≥ 0.1% and <1%)	Immune system disorders	Hypersensitive reactions, including angioneurotic oedema and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Rare (≥0.01% and <0.1%)	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders	Dry skin

1. May be reduced by concomitant castration

2. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.

In patients with advanced prostate cancer, treated with bicalutamide 50 mg in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (49%).

Diarrhea was the adverse event most frequently leading to treatment withdrawal with 6% of patients treated with flutamide-LHRH analogue and 0.5% of patients treated with bicalutamide-LHRH analogue withdrawing.

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 following adverse experiences with an incidence of more than 5%, regardless of causality have been reported.

Incidence Of Adverse Events (≥ 5% In Either Treatment Group) Regardless Of Causality

Adverse Event	Treatment Group Number of Patients (%)			
	Bicalutamide 50 mg Plus LHRH Analogue (N=401)		Flutamide Plus LHRH Analogue (N=407)	
Pain (General)	109	(27)	93	(23)
Constipation	67	(17)	50	(12)
Back Pain	62	(15)	68	(17)
Asthenia	60	(15)	69	(17)
Pelvic Pain	52	(13)	46	(11)
Nausea	44	(11)	45	(11)
Infection	41	(10)	35	(9)
Diarrhea	40	(10)	98	(24)
Nocturia	35	(9)	43	(11)
Peripheral Edema	34	(8)	28	(7)
Abdominal Pain	33	(8)	31	(8)
Dizziness	30	(7)	27	(7)

Dyspnea	30	(7)	24	(6)
Hematuria	30	(7)	20	(5)
Anemia*	29	(7)	35	(9)
Urinary Tract Infection	26	(6)	24	(6)
Increased Liver Enzyme Test#	25	(6)	40	(10)
Rash	25	(6)	20	(5)
Paresthesia	24	(6)	27	(7)
Chest Pain	24	(6)	20	(5)
Sweating	23	(6)	18	(4)
Flatulence	22	(5)	16	(4)
Hypertension	21	(5)	18	(4)
Impotence	20	(5)	29	(7)
Hyperglycaemia	20	(5)	16	(4)
Insomnia	19	(5)	30	(7)
Gynaecomastia	19	(5)	23	(6)
Bone Pain	18	(4)	26	(6)
Headache	17	(4)	20	(5)
Flu Syndrome	16	(4)	20	(5)
Weight Loss	16	(4)	20	(5)
Vomiting	12	(3)	20	(5)
Urinary Incontinence	9	(2)	20	(5)

*Anemia includes anemia, hypochromic- and iron deficiency anemia
#Increased liver enzyme test includes increases in SGPT, SGOT or both.

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians) with a frequency of ≥1 % during treatment with bicalutamide 50 mg plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:

Cardiovascular System: heart failure

Gastrointestinal System: anorexia, dry mouth, dyspepsia, constipation, flatulence

Central Nervous System: dizziness, insomnia, somnolence, decreased libido

Respiratory System: dyspnoea

Urogenital: impotence, nocturia

Hematological: anemia

Skin & Appendages: alopecia, rash, sweating, hirsutism

Metabolic & Nutritional: hyperglycaemia, edema, weight gain, weight loss,diabetes mellitus.

Whole Body: abdominal pain, chest pain, headache, pain, pelvic pain, chills.

Abnormal Laboratory Test Values:

Laboratory abnormalities including elevated SGOT, SGPT, 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 .

SYMPTOMS AND TREATMENT OF 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 AVA-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.

DOSAGE AND ADMINISTRATION

AVA-BICALUTAMIDE 50 mg in metastatic disease: The recommended dose for AVA-BICALUTAMIDE therapy in combination with an LHRH analogue or surgical castration is one 50 mg tablet once daily with or without food. AVA-BICALUTAMIDE treatment should be started at the same time as treatment with an LHRH analogue or after surgical castration.

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 Precautions).

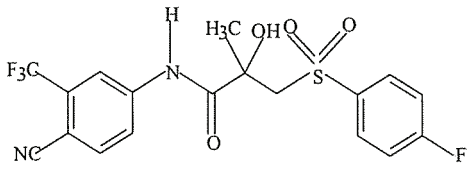
PHARMACEUTICAL INFORMATION

Drug Substance:

Common Name: bicalutamide

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

Structural Formula:



Molecular Weight: 430.37

Description: 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, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran. The pKa is approximately 12. The melting point range is 191-193°C.

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

Composition

In addition to the active ingredient bicalutamide, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, polydextrose, titanium dioxide, hydroxypropyl-methylcellulose, and polyethylene glycol.

Storage Recommendations

Store between 15 - 30°C.

AVAILABILITY OF DOSAGE FORMS

AVA-BICALUTAMIDE 50 mg tablets are white, round, film coated tablets debossed with "**93**" on one side and the other side debossed with "**220**". Available in unit dose blister packs of 30 tablets.

INFORMATION FOR THE CONSUMER

[Pr]AVA-BICALUTAMIDE TABLETS

(bicalutamide 50 mg)

This information applies only to your medicine, AVA-BICALUTAMIDE, please read it carefully. It gives you important information and supplements the information given to you by your doctor. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.

WHAT IS YOUR MEDICINE?

- AVA-BICALUTAMIDE belongs to a group of medicines called anti-androgens. This means that it interferes with some of the actions of androgens (male sex hormones) within the body.
- AVA-BICALUTAMIDE comes in tablets containing 50 milligrams (mg) of bicalutamide as the active ingredient.
- Each tablet contains a number of inactive ingredients which allow it to be made. These are microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, polydextrose, titanium dioxide, hydroxypropyl-methylcellulose, and polyethylene glycol.
- AVA-BICALUTAMIDE comes in bottles of 100 and 500, and unit dose blister packs of 30 tablets.

WHO HAS MADE YOUR MEDICINE?

- Your medicine is made by Avanstra Inc.

WHAT IS YOUR MEDICINE FOR?

- AVA-BICALUTAMIDE 50 mg dose is used to treat advanced prostate cancer in combination with other treatments such as other drugs which reduce the levels of androgens in the body.

WHAT ARE THE STAGES OF PROSTATE CANCER?

- In the early stages, prostate cancer is confined to the prostate gland (localized disease). As the disease progresses the cancer spreads to other tissues within the pelvis (locally advanced disease) and eventually to other parts of the body (advanced or metastatic prostate cancer).

- In recent years, the development of a simple blood test for a protein produced by the prostate (Prostate Specific Antigen; PSA) has made the detection of prostate cancer easier. As a result of PSA testing and greater public awareness, there has been 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.

WHAT SIDE EFFECTS MAY BE EXPERIENCED WITH AVA-BICALUTAMIDE?

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

Contact your doctor or seek medical help immediately if you experience any of the following:

- 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. This side effect is uncommon (1 to 10 in every 1000 patients).
- Severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing. These reactions to bicalutamide 50 mg are uncommon (1 to 10 in every 1000 patients).

Tell your doctor if any of the following side effects bother you:

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

- tender or enlarged breast tissue
- hot flushes

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

- nausea
- diarrhoea
- itching
- feeling weak
- yellow skin and eyes (jaundice)

Side effects that are rare (1 to 10 in every 10,000 patients are likely to have them):

- vomiting
- dry skin

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

Do not be alarmed by this list of possible events. You may not have any of them.

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

WHAT DO YOU NEED TO KNOW ABOUT USING AVA-BICALUTAMIDE?

- 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 AVA-BICALUTAMIDE, your physician may discontinue AVA-BICALUTAMIDE for several weeks in order to monitor your condition off treatment.

WHEN SHOULD AVA-BICALUTAMIDE NOT BE USED?

- AVA-BICALUTAMIDE should not be used in patients with early phase (localized) prostate cancer who would otherwise undergo watchful waiting.
- Before taking your medicine you should tell your doctor if you have previously taken AVA-BICALUTAMIDE and experienced an allergic reaction to it.
- AVA-BICALUTAMIDE must not be taken by women, including pregnant women or mothers who are breast feeding their babies.
- AVA-BICALUTAMIDE must not be given to children.
- The tablets are only for you and must never be given to anyone else.

HOW SHOULD I TAKE MY AVA-BICALUTAMIDE?

- 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.

- You should take AVA-BICALUTAMIDE as prescribed. However, if you miss a dose do not take an extra dose. Just resume your usual schedule.
- If you take more than your normal dose contact your doctor or nearest hospital.
- Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.

WHAT PRECAUTIONS SHOULD BE TAKEN WITH AVA-BICALUTAMIDE?

Before taking your medicine, tell your doctor if:

- you have previously had a reaction to taking AVA-BICALUTAMIDE or any of the ingredients in the product (see WHAT IS YOUR MEDICINE?).
- you are suffering from any disorder or disease which affects your liver.
- you are taking any other medicines including those which you have bought without a prescription.

In particular if you are taking oral anti-coagulants (to prevent blood clots):

- If you go into hospital let the medical staff know you are taking AVA-BICALUTAMIDE
- As mentioned earlier your tablets contain lactose and titanium dioxide which may cause a problem in a small number of patients who are sensitive to them.
- Only stop taking your tablets if your doctor tells you.

Your tablets are unlikely to adversely affect your ability to drive a car or to operate machinery.

HOW SHOULD I STORE AVA-BICALUTAMIDE?

- 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 at room temperature (15 to 30°C).

Customer Inquiries: 1-855-708-3678

medinfo@avanstra.com

Avanstra Inc.
10761 – 25th NE
Suite 110, Building “B”
Calgary, Alberta
T2C 3C2
Canada

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 □/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 variabiIity.

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)-enatiomer to (S)-enatiomer 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 actue 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).

Long-Term Toxicity

SPECIES	DURATION	NO OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
Rat Wistar	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 Ill and IV. Small prostate and seminal vesicles at all doses and reversible, drug related increase in liver weight (21% and 35% for Groups Ill and IV males, 36%, 55% and 90% for Groups Il-IV females) and adrenal weights (24% and 50% for Group Ill and IV males, 16% and 27% for Group Ill 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 Wistar	6 month	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 Ill & 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 these changes were reduced or reversed in the drug withdrawal period - the adrenal cortical vacuolation and castration cells in pituitary were largely unchanged.

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

Long-Term Toxicity (Continued)

SPECIES	DURATION	NO OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
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 Ill & 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 Ill & 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 Ill & 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 hormone-sensitive organs, benign testicular Leydig cell tumours (all dosed groups), thyroid follicular adenomas (Group IV) and uterine carcinomas (Group IV) at the end of the withdrawal period.
Dog Beagle	6 weeks	2 M + 2F	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) at all time points for Groups Ill & IV; there was a mild phenobarbital-like induction of cytochrome P450.

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

Long-Term Toxicity (Continued)

SPECIES	DURATION	NO OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
Dog Beagle	6 months	5-8 M* + 5-8F*	Oral	0, 2.5, 10, 100	Two males (Group Ill & 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.

Long-Term Toxicity (Continued)

SPECIES	DURATION	NO OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
Dog Beagle	12 month	5-8 M* + 5-8 F*	Oral	0, 1, 2.5, 50	There was a decrease in mean P-R interval in Group Ill & 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 Ill & IV; these were anti-androgen related effects. Following 6 months withdrawal there was no compound-related 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 Ill & 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 tumorigenic 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).

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 + 6F	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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