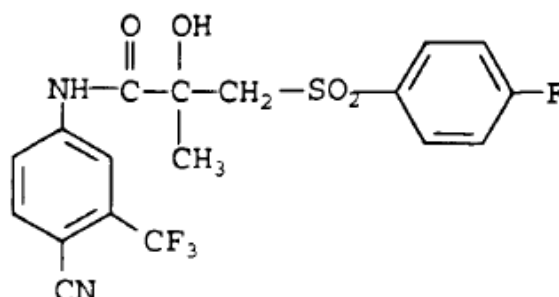


**APO-BICALUTAMIDE 50 MG TABLETS****NAME OF THE MEDICINE**

Bicalutamide.

Chemical Name: (RS)-4'-Cyano- $\alpha$ ',  $\alpha$ ',  $\alpha$ '-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

Structural Formula:

Molecular Formula:  $C_{18}H_{14}F_4N_2O_4S$ 

Molecular Weight: 430.38

CAS Registry Number: 90357-06-5

**DESCRIPTION**

Bicalutamide is a fine white to off-white powder. At 37°C it is practically insoluble in water (4.6 mg/litre), acid (4.6 mg/litre at pH 1) and alkali (3.7 mg/litre at pH 8). In organic solvents it is slightly soluble in ethanol, sparingly soluble in methanol and freely soluble in acetone and tetrahydrofuran.

In addition to bicalutamide, APO-Bicalutamide also contains lactose, sodium starch glycollate, povidone, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

**PHARMACOLOGY****Pharmacodynamics**

Bicalutamide is a non-steroidal anti-androgen, devoid of other endocrine activity. It binds to androgen receptors without activating gene expression, and thus inhibits the androgen stimulus. This inhibition impairs the growth and encourages apoptosis in androgen-dependent tumour cells and regression of prostatic tumours. In a subset of patients who experience disease progression while receiving bicalutamide, discontinuation of the drug may result in an 'anti-androgen withdrawal syndrome', which manifests as a fall in prostate specific antigen (PSA) level. It is unknown whether this phenomenon translates to a prolongation of tumour response or survival.

Bicalutamide is a racemate with its antiandrogenic activity being almost exclusively in the (R)-enantiomer.

**Pharmacokinetics**Absorption

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

Distribution

Bicalutamide is highly protein bound (racemate 96%, R-enantiomer 99.6%).

Steady state plasma concentrations of the (R)-enantiomer of approximately 9 µg per mL are observed during daily administration of 50 mg of bicalutamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

### Metabolism and Elimination

Bicalutamide undergoes stereospecific metabolism. Bicalutamide is extensively metabolised (via oxidation and glucuronidation). Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week. On daily administration of bicalutamide, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half-life.

The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

## **CLINICAL TRIALS**

### **Combination Therapy (with Medical Castration) in Advanced Prostate Cancer**

In a large multicentre, controlled clinical trial, 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 a Luteinising Hormone Releasing Hormone Agonist (LHRH Agonist) (either goserelin acetate implant or leuporelin acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. Bicalutamide / LHRH agonist therapy was associated with a statistically significant ( $p = 0.005$ ) improvement in time to treatment failure.

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 agonists. This small difference was not statistically significant between bicalutamide 50 mg combination therapy and flutamide combination therapy.

### **Meta-Analysis**

There is considerable debate regarding the relative merits of combination versus monotherapy in advanced prostate cancer, summarised by Dalesio et al 1995<sup>1</sup> in their meta-analysis of trials of maximal androgen blockade (MAB). This analysis showed no statistically significant reduction in the annual odds of death in favour of MAB. The meta-analysis included the effect of MAB only on mortality, and did not measure other end-points such as time to disease progression.

## **INDICATIONS**

- Treatment of advanced prostate cancer in combination with LHRH agonist therapy.
- Prevention of disease flare associated with the use of LHRH agonists.

## **CONTRAINDICATIONS**

- Bicalutamide is contraindicated in females and children.
- Known hypersensitivity to bicalutamide or any other constituents of the formulation.
- Co-administration of terfenadine, astemizole or cisapride with bicalutamide is contraindicated (see Interactions with other Medicines).

## **PRECAUTIONS**

Bicalutamide is extensively metabolised in the liver. Data suggests that its elimination 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.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of these changes occur within the first 6 months of bicalutamide therapy.

Rare cases of death or hospitalisation due to severe liver injury have been observed with bicalutamide

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<sup>1</sup> Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. *Lancet* 1995; 346: 265-269.

(see **ADVERSE EFFECTS**). Bicalutamide therapy should be discontinued if at any time a patient develops jaundice or if serum ALT rises above two times the upper limit of normal.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. 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 in patients receiving bicalutamide in combination with LHRH agonists.

In patients with metastatic prostate cancer, treatment with bicalutamide monotherapy has been associated with reduced survival compared to castration. Bicalutamide should therefore not be used without concomitant LHRH agonist therapy in these patients.

### Effects on Fertility

Administration of bicalutamide may lead to inhibition of spermatogenesis. The long-term effects of bicalutamide on male fertility have not been studied. In male rats dosed at 250 mg/kg/day (less than human therapeutic concentrations after the maximum recommended clinical dose of 150 mg), 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 11-week period of dosing.

### Use in Pregnancy (Category D)<sup>2</sup>

Bicalutamide is contraindicated in females and must not be given to pregnant women.

### Use in Lactation

Bicalutamide is contraindicated in females and must not be given to breast-feeding mothers.

### Carcinogenicity

Two-year oral carcinogenicity studies were conducted in male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide. 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 male rats at all dose levels and uterine adenocarcinoma in female rats at 75 mg/kg/day (at these dose levels plasma (R)-bicalutamide concentrations were less than human therapeutic concentrations after the maximum recommended clinical dose of 150 mg). There is no evidence of Leydig cell hyperplasia in patients; uterine tumours are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 2 times human therapeutic concentrations after the maximum recommended clinical dose of 150 mg) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (less than the human therapeutic concentrations after the maximum recommended clinical dose of 150 mg) 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.

### Genotoxicity

Bicalutamide was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

## INTERACTIONS WITH OTHER MEDICINES

Bicalutamide is extensively metabolised (via oxidation and glucuronidation) in the liver. Bicalutamide has shown no evidence of causing enzyme induction in humans during dosing at 50 mg daily in man. *In vitro* studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

The clinically or potentially significant drug interactions between bicalutamide and the following agents/drug classes, which are theoretical or have been observed, are described below. The drug/drug interactions described include both interactions mediated through effects on P450 metabolism and interactions mediated through other mechanisms.

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<sup>2</sup> Category D - Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details

## Effects of Bicalutamide on Other Medicines

### LHRH agonists

Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide 50 mg and LHRH agonists at steady state, bicalutamide 50 mg may prevent the harmful clinical consequences of flare associated with the start of LHRH agonist therapy.

### Cytochrome P450

Bicalutamide is an inhibitor of CYP 3A4 and has been shown to increase plasma levels of midazolam by up to 80 %. Therefore, concomitant use of terfenadine, astemizole and cisapride is contraindicated. Caution should be exercised with other drugs metabolised by CYP 3A4, such as cyclosporin, calcium channel blockers, HIV antivirals, HMGCoA reductase inhibitors, carbamazepine, quinidine etc.

## Demonstrated Interactions

### Warfarin

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

## Theoretical Interactions

Caution should be exercised when prescribing bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide and an increase in adverse effects.

## Effects on Ability to Drive and Use Machines

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

## ADVERSE EFFECTS

Bicalutamide 50 mg in general, has been well tolerated with few withdrawals due to adverse events.

Bicalutamide 50 mg may be associated with the occurrence of diarrhoea and vomiting.

## Clinical Trial Data

### Combination Therapy (with Medical Castration) in Advanced Prostate Cancer

The following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of  $\geq 1\%$ ) during treatment with bicalutamide 50 mg plus an LHRH agonist. 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.

Adverse events within each body system are listed in descending order of frequency (Very common:  $\geq 10\%$ ; Common:  $\geq 1\%$  and  $< 10\%$ ; Uncommon:  $\geq 0.1\%$  and  $< 1\%$ ; Rare:  $\geq 0.01\%$  and  $< 0.1\%$ ; Very Rare:  $< 0.01\%$ ).

These include the following:

### **Very Common**

*Blood and lymphatic system:* anaemia

*Nervous system disorders:* dizziness

*Vascular disorder:* hot flush <sup>1</sup>

*Gastrointestinal disorders:* abdominal pain, constipation, nausea

*Renal and urinary disorders:* haematuria

*Reproductive system and breast disorders:*  
breast tenderness<sup>1</sup>, gynaecomastia<sup>1</sup>

*General disorders and administration site conditions:*  
asthenia, chest pain, oedema

**Common***Metabolism and nutrition disorders:*

decreased appetite

*Psychiatric disorders:*

decreased libido, depression

*Cardiac Disorders:*myocardial infarction (fatal outcomes have been reported)<sup>3</sup>, cardiac failure<sup>3</sup>*Gastrointestinal disorders:*

anorexia, dry mouth, dyspepsia, flatulence

*Nervous system disorders:*

insomnia, somnolence

*Hepato-biliary disorders:*hepatotoxicity, jaundice, hypertransaminasaemia<sup>2</sup>*Respiratory System*

dyspnoea

*Urogenital*

impotence, nocturia

*Skin and Subcutaneous Tissue disorders:*alopecia, rash, sweating, hirsutism / hair re-growth, dry skin, pruritis<sup>1</sup>*Metabolic and Nutritional disorders:*

diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss, decreased appetite

*Whole Body*

abdominal pain, headache, pain, pelvic pain, chills

*Reproductive system and breast disorders*

erectile dysfunction

**Uncommon***Immune system disorders:*

hypersensitivity reactions, angioedema, and urticaria

*Respiratory, thoracic and mediastinal disorders*interstitial lung disease (ILD)<sup>4</sup> - fatal outcomes have been reported.**Rare***Hepato-biliary disorders:*hepatic failure<sup>5</sup> - fatal outcomes have been reported.<sup>1</sup> May be reduced by concomitant castration<sup>2</sup> Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy<sup>3</sup> Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appears to be increased when bicalutamide 50 mg was used in combination with LHRH agonists but no increase in risk was evident when bicalutamide 150 mg was used as a monotherapy to treat prostate cancer.<sup>4</sup> Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies<sup>5</sup> Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open-label bicalutamide arm of the 150 mg EPC studies

## **DOSAGE AND ADMINISTRATION**

### **Adult Males Including the Elderly**

One tablet (50 mg) once a day.

Treatment with bicalutamide 50 mg should be started at the same time as treatment with a LHRH agonist.

### Use in Adult Males with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

### Use in Adult Males with Hepatic Impairment

No dosage adjustment is necessary for patients with mild hepatic impairment.

Increased accumulation may occur in patients with moderate to severe hepatic impairment (see **PRECAUTIONS**). In such cases, a lower or less frequent dose may be considered.

## **OVERDOSAGE**

### **Symptoms**

There is no human experience of overdosage.

### **Treatment**

There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

**Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.**

## **PRESENTATION AND STORAGE CONDITIONS**

**APO-Bicalutamide 50 mg tablets:** White to off white, round, biconvex, film coated tablets debossed "B50" on one side and plain on other side.

Blister pack of 28 tablets.

APO-Bicalutamide 50 mg tablets are intended for oral administration.

Each tablet contains bicalutamide 50 mg as the active ingredient.

Store below 25°C. Protect from moisture.

## **NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
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Macquarie Park NSW 2113

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## **POISONS SCHEDULE OF THE MEDICINE**

S4 - Prescription Only Medicine.

**Date of first inclusion in the Australian register of Therapeutic Goods (ARTG):** 13 April 2012