AUSTRALIAN PRODUCT INFORMATION

COSAMIDE® 50

(bicalutamide) tablets

1 NAME OF THE MEDICINE

Bicalutamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COSAMIDE 50 tablet contains 50 mg of bicalutamide as the active ingredient.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The tablets are white to off white, round, biconvex, film-coated tablets debossed "B50" on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of advanced prostate cancer in combination with Luteinising Hormone Releasing Hormone (LHRH) agonist therapy.

Prevention of disease flare associated with the use of LHRH agonists.

4.2 DOSE AND METHOD OF 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.

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In such cases, a lower or less frequent dose may be considered.

4.3 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperglycaemia

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.

Potentiation of coumarin anticoagulant effects

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant bicalutamide therapy, which may result in increased Prothrombin Time (PT) and International Normalised Ratio (INR). Some cases have been associated with risk of bleeding. Close monitoring of PT/INR is advised and anticoagulant dose adjustment should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in patients with metastatic prostate cancer

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.

QT/QTc interval prolongation

Androgen deprivation therapy may prolong QT/QTc interval. Prescribers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte imbalances should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Use in hepatic impairment

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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Use in renal impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in the elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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 medicines metabolised by CYP 3A4, such as ciclosporin, 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. There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with bicalutamide. It is therefore recommended that if bicalutamide is administered in patients who are already receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Theoretical interactions

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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. Atrophy of seminiferous tubules of the testes, atrophy of the epididymis, and atrophy of the male reproductive glands are predicted class effects of antiandrogens and have been observed in rats at exposures less than the therapeutic concentrations at the recommended clinical dose of 50 or 150 mg. Reversal of seminiferous tubule and seminal vesicle atrophy occurred in most animals by 4 months after the completion of dosing in a 6-month rat study. In this study, prostate atrophy was not fully reversible by 4 months after the completion of dosing. No recovery of seminiferous tubule atrophy was observed at 24 weeks after the completion of dosing in a 12-month rat study. Following 12 months of repeated dosing in dogs, the incidence of testicular atrophy was the same in dosed and control dogs after a 6-month recovery period. In male rats dosed at 250 mg/kg/day (less than human therapeutic concentrations after the recommended clinical dose of 50mg or 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. A period of subfertility or infertility should be assumed in man.

Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effect of bicalutamide on sperm morphology has not been evaluated and no such changes have been reported for patients who received bicalutamide, patients and/or their partners should follow adequate contraception during bicalutamide therapy and for 130 days after bicalutamide therapy.

Use in pregnancy (Category D)

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.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Clinical trial data – Combination therapy (with medical castration) in advanced prostate cancer

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

Table 1: Bicalutamide adverse drug effects by frequency and System Organ Class

Frequency	System Organ Class	Event
Very Common (≥10%)	Blood and lymphatic	anaemia
	Nervous system disorders	dizziness
	Vascular disorder	hot flush
	Gastrointestinal disorders	abdominal pain, constipation, nausea
	Renal and urinary disorders	haematuria
	Reproductive system and breast disorders	breast tenderness[1], gynaecomastia[1]
	General disorders and administration site conditions	asthenia, chest pain, oedema
Common (≥1% - <10%)	Metabolism and nutrition disorders	decreased appetite (anorexia)
	Psychiatric disorders	decreased libido, depression

	Nervous system disorders	somnolence
	Gastrointestinal disorders	dyspepsia, flatulence
	Hepato-biliary disorders	hepatotoxicity, jaundice, hypertransaminasaemia[2]
	Cardiac disorders	myocardial infarction (fatal outcomes have been reported)[3], cardiac failure[3]
	Skin and subcutaneous tissue disorders	alopecia, hirsutism/ hair regrowth, rash, dry skin, pruritus
	Reproductive system and breast disorders	erectile dysfunction
	Investigations	weight increased
Uncommon (≥0.1% - <1%)	Immune system disorders	hypersensitivity reactions, angiodema and urticaria
	Respiratory, thoracic and mediastinal disorders	interstitial lung disease (ILD)[4] - fatal outcomes have been reported
Rare (≥0.01% - <0.1%)	Hepato-biliary disorders	hepatic failure[5] - fatal outcomes have been reported
	Skin and subcutaneous tissue disorders	photosensitivity reaction

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

3 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 tablets 50 mg was used in combination with LHRH agonists but no increase in risk was evident when Bicalutamide tablets 150 mg was used as a monotherapy to treat prostate cancer.

4 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

5 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

Increased PT/INR: Accounts of coumarin anticoagulants interacting with bicalutamide have been reported in post marketing surveillance (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

There is no human experience of overdosage. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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 medicine 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 anti-androgenic activity being almost exclusively in the (R)-enantiomer.

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 randomised 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 leuprorelin 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[1] 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.

5.2 PHARMACOKINETIC PROPERTIES

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%).

1 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.

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

Metabolism

Bicalutamide undergoes stereospecific metabolism. Bicalutamide is extensively metabolised (via oxidation and glucuronidation).

Excretion

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.

Special populations

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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 anti-androgenicity 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

COSAMIDE 50 tablets contain: lactose monohydrate, sodium starch glycollate type A, povidone, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in blister packs (PVC/PVDC/Al) of 28 tablets.

Australian Register of Therapeutic Goods (ARTG)

AUST R 162829 - COSAMIDE 50 bicalutamide 50mg film-coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

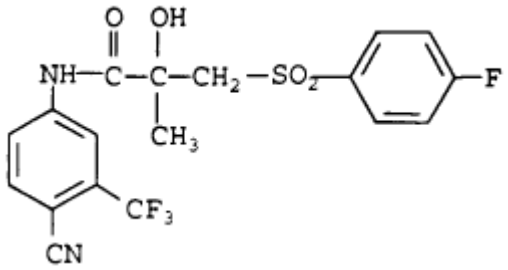
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : (RS)-4'-Cyano-α', α', α',-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide

Propanamide,N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+-).

Structural formula :



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

Molecular weight : 430.38

CAS Number

90357-06-5

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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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9 DATE OF FIRST APPROVAL

23/07/2010

10 DATE OF REVISION

26/05/2023

Summary Table of Changes

Section Changed	Summary of New Information
2, 6.1	Minor editorial changes Move physiochemical properties to Section 6.7
6.5	Insert AUST R numbers
8	Update sponsor's details

COSAMIDE 50_pi\May23/01