AUSTRALIAN PRODUCT INFORMATION

COSUDEX® (bicalutamide) TABLETS

1 NAME OF THE MEDICINE

Bicalutamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COSUDEX tablet contains 50 mg bicalutamide.

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.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Round, biconvex, white film-coated tablet impressed with Cdx50 on one side and an arrow shaped logo on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of advanced prostate cancer in combination with 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 COSUDEX 50 mg should be started at the same time as treatment with a luteinising hormone releasing hormone (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

COSUDEX is contraindicated in females and children.

Known hypersensitivity to bicalutamide or any other constituents of the formulation.

Coadministration of terfenadine, astemizole or cisapride with COSUDEX 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 COSUDEX in combination with LHRH agonists.

Potentiation of coumarin anticoagulant effects

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant COSUDEX 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 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 gonadotropin-releasing hormone (GnRH) 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.

Interstitial lung disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with COSUDEX, including fatal cases. If ILD is diagnosed, treatment with COSUDEX should be discontinued and appropriate treatment should be considered (see Section 4.8 Adverse effects (Undesirable effects)).

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 alanine aminotransferase (ALT) rises above two times the upper limit of normal (ULN).

Use in the elderly

No data available.

Paediatric use

No data available. COSUDEX is contraindicated in children (see Section 4.3 Contraindications).

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 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.

Effects of bicalutamide on other medicines

LHRH agonists: Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH agonists at steady state, bicalutamide 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. There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with COSUDEX. It is therefore recommended that if COSUDEX 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 COSUDEX with other drugs which may inhibit drug oxidation eg cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide and an increase in adverse reactions.

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 50 mg 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 COSUDEX, patients and/or their partners should follow adequate contraception during COSUDEX therapy and for 130 days after COSUDEX therapy.

Use in pregnancy – Category D

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

Use in lactation

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

COSUDEX 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 drug reactions in the opinion of investigating clinicians, with a frequency of ≥1%) during treatment with COSUDEX 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.

Table 1: COSUDEX adverse drug reactions by frequency and System Organ Class

Frequency	System Organ Class	Event
Very common (≥10%)	*Blood & lymphatic*	anaemia
	Nervous system disorders	dizziness
	Vascular disorder	hot flush
	Gastrointestinal disorders	abdominal pain, constipation, nausea
	Renal and urinary disorders	haematuria
	Reproductive system & breast disorders	breast tenderness [a], gynaecomastia [a]
	General disorders & administration site conditions	asthenia, chest pain, oedema
Common (≥1%-<10%)	*Metabolism & nutrition disorders*	decreased appetite
	Psychiatric disorders	decreased libido, depression
	Nervous system disorders	somnolence
	Gastrointestinal disorders	dyspepsia, flatulence
	Hepatobiliary disorders	hepatotoxicity, jaundice, hypertransaminasaemia [b]
	Cardiac disorders	myocardial infarction [c, d], cardiac failure [d]
	Skin & subcutaneous tissue disorders	alopecia, hirsuitism/ hair re-growth, rash, dry skin, pruritis
	Reproductive system & breast disorders	erectile dysfunction
	Investigations	weight increased
Uncommon (≥0.1%-<1%)	*Immune system disorders*	hypersensitivity reactions, angioedema, urticaria
	Respiratory, thoracic & mediastinal disorders	interstitial lung disease (ILD) [c,e]
Rare (≥0.01%-<0.1%)	*Hepatobiliary disorders*	hepatic failure [c,f]
	Skin & subcutaneous tissue disorders	Photosensitivity reaction

[a] May be reduced by concomitant castration

[b] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy

[c] Fatal outcomes have been reported

[d] Observed in a pharmacoepidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appears to be increased when COSUDEX 50 mg was used in combination with LHRH agonists but no increase in risk was evident when COSUDEX 150 mg was used as a monotherapy to treat prostate cancer.

[e] 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

[f] 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 COSUDEX arm of the 150 mg EPC studies

Increased PT/INR: Accounts of coumarin anticoagulants interacting with COSUDEX 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 Poison Information Centre on 131126 (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 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 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 COSUDEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with a Luteinising Hormone Releasing (LHRH) (either goserelin acetate implant or leuprorelin acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. COSUDEX/ 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 COSUDEX and in 88 (54%) patients treated with flutamide, each in combination therapy with LHRH agonists. This small difference was not statistically significant between COSUDEX 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 [a] 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.

[a] 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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

COSUDEX 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 COSUDEX 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 COSUDEX, 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

Each COSUDEX tablet contains the following excipients: lactose monohydrate, sodium starch glycollate, povidone, magnesium stearate, hypromellose, macrogol 300 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 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

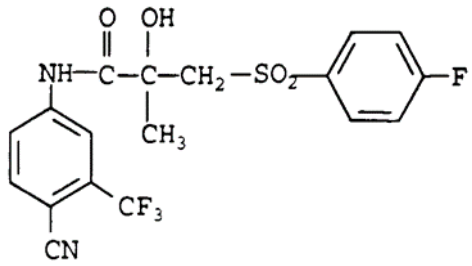
COSUDEX 50 mg tablets are packed in PVC/aluminium blisters in packs of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



(RS)-4'-Cyano-α', α', α',-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-m-toluidide.

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

Molecular weight: 430.38

CAS number

90357-06-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 July 1996

10 DATE OF REVISION

9 July 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	New precaution for interstitial lung disease (ILD)
Various	Minor editorial/format updates

COSUDEX® is a trademark of the AstraZeneca group of companies.

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