AUSTRALIAN PRODUCT INFORMATION

ZOLACOS® CP
(bicalutamide tablets and goserelin implant)

1 NAME OF THE MEDICINE

Bicalutamide and goserelin acetate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOLACOS is a combination pack containing COSUDEX® and ZOLADEX®.

Each COSUDEX (bicalutamide) tablet contains 50 mg bicalutamide. Each ZOLADEX implant contains goserelin 3.6 mg or 10.8 mg (as goserelin acetate).

Excipients with known effect: Each COSUDEX tablet contains lactose monohydrate.

For the full list of excipients for COSUDEX and ZOLADEX, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

COSUDEX are white, round, biconvex film-coated tablets, impressed with CDX50 on one side and an arrow shaped logo on the other side.

ZOLADEX is a sterile white to cream coloured cylindrical implant.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of advanced prostate cancer.

Bicalutamide is also indicated for the prevention of disease flare associated with initial goserelin treatment.

4.2 Dose and method of administration

Adult males including the elderly

Bicalutamide

One tablet (50 mg) once a day.

Treatment with COSUDEX 50 mg should be started at the same time as treatment with a Gonadotrophin Releasing Hormone agonist (GnRH agonist).

Goserelin

Caution should be taken while inserting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches. Do not penetrate into muscle or peritoneum.

The ZOLADEX syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the

needle and immediately control any resultant bleeding, monitoring the patient for signs or symptoms of abdominal haemorrhage. After ensuring the patient is haemodynamically stable another ZOLADEX implant may be injected with a new syringe elsewhere.

Use extra care when administering ZOLADEX to patients with a low BMI and/or who are receiving full anticoagulation medication (see Section 4.4 Special warnings and precautions for use).

One 3.6 mg implant of goserelin every 28 days or one 10.8 mg implant of goserelin every 3 months, injected subcutaneously into the anterior abdominal wall.

Before injection, it should be ensured that the implant is visible in the window of the applicator. The plunger should not be withdrawn once the needle is in position. The plunger should be fully depressed to expel the implant into subcutaneous tissue well away from point of entry and to activate the protective needle sleeve.

For correct administration of goserelin, see instructions on the administration card.

Do not omit or delay injections, as serum testosterone levels may rise.

In the unlikely event of the need to surgically remove a ZOLADEX implant, it may be localised by ultrasound.

Elderly

No dosage adjustment is necessary in the elderly.

Use in patients with renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with mild hepatic impairment. Increased accumulation of bicalutamide 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

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).

Goserelin

Goserelin is contraindicated in patients with known hypersensitivity to GnRH or GnRH agonist analogues or any of the components of ZOLADEX.

4.4 Special warnings and precautions for use

Bicalutamide

Hyperglycaemia

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving COSUDEX in combination with a GnRH agonist and manage with current practice for the treatment of hyperglycaemia or diabetes.

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 Section 4.5 Interactions with other medicines and other forms of interactions).

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 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 GnRH agonist therapy in these patients.

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.

Goserelin

Injection site injury

Injection site injury has been reported with ZOLADEX, including events of pain, haematoma, haemorrhage and vascular injury. Monitor affected patients for signs or symptoms of abdominal haemorrhage. In very rare cases, administration error resulted in vascular injury and haemorrhagic shock requiring blood transfusions and surgical intervention.

Patients with low BMI and/or receiving full anticoagulation medications

Extra care should be taken when administering ZOLADEX to patients with a low BMI and/or receiving full anticoagulation medications (see Section 4.2 Dose and method of administration).

Effects on bone

Goserelin may cause a temporary increase in bone pain in patients with advanced cancer and bone metastases which may last for up to two weeks.

Goserelin causes loss of bone mineral density.

Ureteric obstruction or spinal cord compression

Goserelin may also increase the risk of developing ureteric obstruction or spinal cord compression in patients with metastatic cancer during the initial month of therapy. The use of goserelin in patients at risk should be considered carefully and patients monitored closely during the first month of therapy.

The above events may be related to the transient increase in serum testosterone concentration with goserelin. The use of antiandrogen therapy at the start of goserelin therapy has been reported to prevent the possible sequelae of the initial rise in serum testosterone.

Injection omission or delay

Serum testosterone concentrations in males may rise if an implant is omitted or delayed.

Hyperglycaemia

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for the treatment of hyperglycaemia or diabetes.

Cardiovascular disease

An increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and managed according to current clinical practice.

QT/QTc interval prolongation

See bicalutamide above.

Use in the elderly

No dosage adjustment is necessary in the elderly.

Paediatric use

COSUDEX is contraindicated in children.

ZOLADEX is not indicated for use in children as safety and efficacy have not been established in this group of patients.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Bicalutamide

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

GnRH agonists: Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and GnRH agonists at steady state, bicalutamide may prevent the harmful clinical consequences of flare associated with the start of GnRH 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 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).

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 reactions.

Goserelin

No data available.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of goserelin with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de Pointes should be carefully evaluated (see Section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Effects on fertility

Bicalutamide

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.

Goserelin

The expected pharmacology of goserelin is the suppression of gonad function to castrate levels. As a result, there is profound impairment of fertility. In rats, this is expressed as:

- *Male*: decrease in weight and atrophic histological changes in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis.
- *Female*: suppression of ovarian function with decreased size and weight of the ovaries and secondary sex organs; arrest of follicular development at the antral stage and reduction in size and number of the corpora lutea.

Except for the testes, almost complete reversal of these effects in male and female rats was observed several weeks after dosing was stopped, however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued.

Based on histological examination, drug effects on reproductive organs seem to be completely reversible in male and female dogs when drug treatment was stopped after continuous administration for 1 year at doses equivalent to 214 µg/kg/day (approximately 57 times the recommended monthly dose for a human based on AUC).

Use in pregnancy – Category D

ZolaCos CP 3.6/50 and 10.8/50 are not indicated in females. (NOTE: Bicalutamide is contraindicated in females – see Section 4.3 Contraindications).

Use in lactation

ZolaCos CP 3.6/50 and 10.8/50 are not indicated in females. (NOTE: Bicalutamide is contraindicated in females – see Section 4.3 Contraindications).

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.

There is no evidence that goserelin results in impairment of ability to drive or operate machinery.

4.8 Adverse effects (Undesirable effects)

In general, combination treatment 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 a Luteinising Hormone Releasing Hormone agonist (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 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
	Psychiatric disorders	Decreased libido, depression
	Nervous system disorders	Somnolence
	Gastrointestinal disorders	Dyspepsia, flatulence
	Hepato-biliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia[2]
	Skin and subcutaneous tissue disorders	Alopecia, hirsuitism/ hair re-growth, rash, dry skin, pruritis
	Reproductive system and breast disorders	Erectile dysfunction
	Cardiac disorders	Cardiac failure[3], myocardial infarction (fatal outcomes have been reported)[3]
	Investigations	Weight increased

Frequency	System Organ Class	Event
Uncommon (≥0.1% - <1%)	*Immune system disorders*	Hypersensitivity reactions, angioedema, 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 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.

[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 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 interaction and Section 4.4 Special warnings and precautions for use).

Goserelin

The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from ZOLADEX clinical trials and post-marketing sources.

Table 2 Goserelin adverse drug reactions by frequency and System Organ Class

Frequency	System Order Class	Event (Males)
Very Common (≥10%)	*Psychiatric disorders*	Libido decreased[a]
	Vascular disorders	Hot flush[a], blood pressure abnormal[c]
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a]
	Reproductive system and breast disorders	Erectile dysfunction, breast tenderness, gynaecomastia
	Nervous system disorders	Paraesthesia
	Investigations	Bone density decreased
Common (≥ 1% and <10%)	*Metabolism and nutrition disorders*	Glucose tolerance impaired[b]
	Renal and urinary tract disorders	Incontinence and urinary frequency (after radiotherapy)
	Nervous system disorders	Spinal cord compression
	Cardiac disorders	Cardiac failure[f] , myocardial infarction[f]
	Skin and subcutaneous tissue disorders	Rash[d]
	Musculoskeletal, connective tissue and bone disorders	Bone pain[e], arthralgia

Frequency	System Order Class	Event (Males)
	General disorders and administration site conditions	Injection site reaction
	Investigations	Weight increased
	Psychiatric disorders	Mood swings
Uncommon (≥0.1% and <1%)	*Immune system disorders*	Drug hypersensitivity
	Renal and urinary tract disorders	Ureteric obstruction
Rare (≥0.01% and <0.1%)	*Immune system disorders*	Anaphylactic reaction
	Endocrine disorders	Pituitary haemorrhage/Infarction
Very rare (<0.01%)	*Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Pituitary tumour
	Psychiatric disorders	Psychotic disorder
Unknown	*Skin and subcutaneous tissue disorders*	Alopecia[g]

[a] These are pharmacological effects which seldom require withdrawal of therapy.
[b] 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 mellitus.
[c] These may manifest as hypotension or hypertension, have been occasionally observed in patients administered ZOLADEX. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with ZOLADEX. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from ZOLADEX
[d] These are generally mild, often regressing without discontinuation of therapy.
[e] Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.
[f] Observed in a pharmaco-epidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.
[g] Particularly loss of body hair, an expected effect of lowered androgen levels

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).

Bicalutamide

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.

Goserelin

There is limited experience of overdosage in humans. In cases where goserelin has unintentionally been readministered early or given at a higher dose, no clinically relevant adverse effects have been seen. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentrations and on the reproductive tract will be evident with higher doses of goserelin. If overdosage occurs, this should be managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Bicalutamide

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.

Goserelin

Goserelin acetate is a synthetic analogue of GnRH. When administered to males, it initially stimulates secretion of luteinising hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland with subsequent increase in serum testosterone concentration. Chronic administration leads to sustained suppression of pituitary gonadotrophins and consequent reduction in serum testosterone concentration to the level normally seen in surgically castrated men within three weeks. This suppression is maintained as long as therapy is continued and can lead to accessory sex organ regression.

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 GnRH Agonist (either goserelin acetate implant or leuprorelin acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. Bicalutamide/ GnRH 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 GnRH agonists. This small difference was not statistically significant between bicalutamide combination therapy and flutamide combination therapy. In an analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with bicalutamide-GnRH agonist therapy and 235 (57.5%) patients treated with flutamide-GnRH agonist therapy had died. There was no significant difference in survival between treatment groups. The hazard ratio for time to death (survival) was 0.87 (95% CI 0.72 to 1.05).

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

Bicalutamide

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 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

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.

Goserelin

ZOLADEX implants release goserelin acetate continuously. After administration of the 3.6 mg implant, the peak serum concentration is not reached until about 2 weeks later whereas after the 10.8 mg implant, the peak serum concentration occurs within 24 hours. There is considerable variability in serum goserelin concentration, the peak concentration varying up to 5-fold after the 3.6 mg and 10-fold after the 10.8 mg implant.

[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.

Although bioavailability from the implants is variable, drug is released at effective concentrations to sustain suppression of serum testosterone concentration for at least 28 days with goserelin 3.6 mg and 3 months with goserelin 10.8 mg. Goserelin is poorly protein bound (20–28%).

Serum goserelin concentration becomes low by day 28 in the case of the 3.6 mg implant and 3 months in the case of the 10.8 mg implant. Delaying or omitting scheduled doses should be avoided since it may lead to increased serum testosterone levels and loss of efficacy.

There is no evidence of significant drug accumulation when ZOLADEX 3.6 mg is administered at 4-weeks intervals and ZOLADEX 10.8 mg at 3-month intervals.

Goserelin is cleared mainly by metabolism. The serum elimination half-life is approximately 4 hours. Dosage adjustment is not required in renal or hepatic impairment.

5.3 Preclinical safety data

Bicalutamide

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 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.

Goserelin

Genotoxicity

Mutagenicity tests for gene mutations and chromosomal damage have provided no evidence for mutagenic effects.

Carcinogenicity

After subcutaneous implant injections once every 4 weeks for 1 year to male and female rats at doses equivalent to 4 times the recommended monthly dose for a human (based on AUC), an increased incidence of benign pituitary microadenomas was found.

This finding is similar to that previously noted in this species following surgical castration and appears to be a species specific response to castration. Any relevance to humans has not been established. No increase in pituitary adenomas was seen in mice receiving injections of goserelin every 3 weeks for 2 years at doses up to 2400 µg/kg/day (approximately 18 to 37 times the recommended monthly dose for a human [based on C_{max}]). An increased incidence of histiocytic sarcomas of the bone marrow of the vertebral column and femur were observed in male mice given 2400 µg/kg/day but not in female mice, or rats of either sex. The relevance of these tumours to humans has not been established.

In mice, long-term repeated dosing with multiples of the human dose produced histological changes in some regions of the digestive system manifested by pancreatic islet cell hyperplasia and a benign proliferation condition in the pyloric region of the stomach, also reported as a spontaneous lesion in this species. The clinical relevance of these findings is unknown.

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.

Each ZOLADEX implant contains the excipient polyglactin.

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.

6.5 Nature and contents of container

ZolaCos CP is available in three different packs:

- 1x ZOLADEX 3.6 mg implant syringe + 28 (1 month) tablets COSUDEX 50 mg
- 1x ZOLADEX 10.8 mg implant syringe + 28 (1 month) tablets COSUDEX 50 mg
- 1x ZOLADEX 10.8 mg implant syringe + 84 (3 month) tablets COSUDEX 50 mg (3 x 28 tablet packs)

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

ZOLADEX SAFESYSTEM® implant is supplied in a pre-filled syringe applicator for subcutaneous injection with a styrene-butadiene plastic copolymer implant chamber in packs of 1 implant.

6.6 Special precautions for disposal

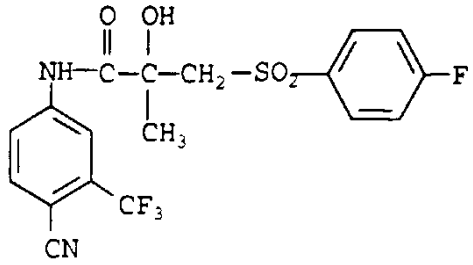
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

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.

Chemical structure

Bicalutamide

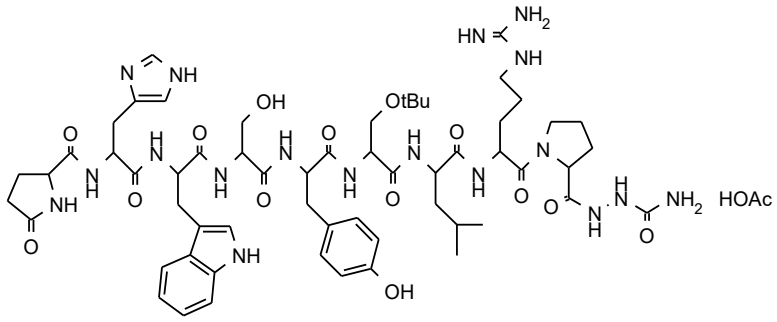


(RS)-4'-Cyano-α', α', α',-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-m-toluidide.

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

Molecular weight: 430.38

Goserelin (as acetate)



Goserelin acetate

Molecular Formula: $C_{59}H_{84}N_{18}O_{14}$ (base)

Molecular Weight: 1269 (base)

CAS number

Bicalutamide

90357-06-5

Goserelin

65807-02-5 (goserelin base)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 December 2006

10 DATE OF REVISION

8 July 2026

Summary table of changes

Section changed	Summary of new information
4.2	Addition of information on administration of goserelin implant.
4.4	New precaution for interstitial lung disease (ILD).
4.5	Use of goserelin with medicinal products known to prolong the QT interval.

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