

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

ZOLACOS CP

Goserelin (present as goserelin acetate) 3.6 mg or 10.8 mg injection + bicalutamide 50 mg tablets.

PRESENTATION

ZOLACOS CP is a combination therapy containing Zoladex (goserelin) 3.6 mg or 10.8 mg subcutaneous implant plus Cosudex (bicalutamide) 50 mg tablets.

BICALUTAMIDE

COSUDEX 50 mg is a white film-coated tablet containing 50 mg bicalutamide and is impressed with CDX50 on one side and a logo on the other.

GOSERELIN

A sterile, white to cream coloured cylindrical implant in which goserelin acetate (equivalent to 3.6 mg or 10.8 mg of peptide base) is dispersed in a biodegradable matrix. It is supplied in a single dose syringe applicator. The SafeSystem™ incorporates a protective needle sleeve that automatically locks in place following administration of the implant to aid in the prevention of needle stick injury.

USES

ACTIONS

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. Regression of prostatic tumours results from this inhibition. Clinically, discontinuation of Bicalutamide can result in antiandrogen withdrawal syndrome in a subset of patients.

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

Goserelin

Goserelin (d-Ser(But)⁶Azgly¹⁰ LHRH) is a synthetic analogue of naturally occurring luteinising-hormone releasing hormone (LHRH). On chronic administration Goserelin results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males. Initially, Goserelin, like other LHRH agonists, may transiently increase serum testosterone concentration in men.

By around 21 days after the first implant injection, testosterone concentrations have decreased to within the castrate range and remain suppressed with continuous treatment.

PHARMACOKINETICS

Bicalutamide

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

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.

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

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.

Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of R-bicalutamide in semen of men receiving bicalutamide 150 mg was 4.9 µg/mL. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 µg/kg. This is below that required to induce changes in offspring of laboratory animals.

Goserelin

3.6 mg

The bioavailability of ZOLADEX 3.6 mg is almost complete. The implant formulation of ZOLADEX 3.6 mg releases the medicine continuously with peak serum concentrations occurring approximately two weeks after administration. Administration of an implant every four weeks ensures that effective concentrations are maintained with no tissue accumulation.

ZOLADEX 3.6 mg is poorly protein bound and has a serum elimination half-life of two to four hours in subjects with normal renal function.

The half-life is increased in patients with impaired renal function. For the compound given monthly in an implant formulation this change will have minimal effect. Hence, no change in dosing is necessary in these patients.

There is no significant change in pharmacokinetics in patients with hepatic failure.

10.8 mg

Administration of ZOLADEX 10.8 mg in accordance with the dosage recommendations ensures that exposure to goserelin is maintained with no clinically significant accumulation. ZOLADEX is poorly protein bound and has a serum elimination half-life of 2 to 4 hours in subjects with normal renal function. The half-life is increased in patients with impaired renal function. For the compound given, as recommended in a 10.8 mg depot formulation, this change will not lead to any accumulation. Hence, no change in dosing is necessary in these patients. There is no significant change in pharmacokinetics in patients with hepatic failure.

INDICATIONS

ZOLACOS CP is indicated for the treatment of advanced prostate cancer and prevention of disease flare associated with the use of LHRH agonists.

DOSAGE AND ADMINISTRATION

ADULT MALES INCLUDING THE ELDERLY

Bicalutamide (Cosudex): One tablet (50 mg) once a day.

Treatment with Cosudex should be started at the same time as treatment with Zoladex.

Goserelin (Zoladex):

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.

CHILDREN

ZOLACOS CP is contraindicated in children.

RENAL AND HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with renal or hepatic impairment.

Increased accumulation of bicalutamide may occur in patients with moderate to severe hepatic impairment (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

BICALUTAMIDE

Bicalutamide is contraindicated in females and children.

Bicalutamide must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients.

GOSERELIN

Known severe hypersensitivity to the active substance or to any of the excipient of this product.

WARNINGS AND PRECAUTIONS

BICALUTAMIDE

Bicalutamide is extensively metabolised in the liver. Data suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, COSUDEX 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.

Severe hepatic changes and hepatic failure have been observed rarely with bicalutamide and fatal outcomes have been reported (see ADVERSE EFFECTS). COSUDEX therapy should be discontinued if changes are severe.

GOSERELIN

The use of ZOLADEX in men at particular risk of developing ureteric obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. If spinal cord compression or renal impairment due to ureteric obstruction are present or develop, specific standard treatment of these complications should be instituted. Isolated cases have been reported.

Initially ZOLADEX, like other LHRH agonists, transiently increases serum testosterone. Some patients may experience a temporary increase in bone pain, which can be managed symptomatically.

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. Consideration should therefore be given to monitoring blood glucose.

An increased risk of developing myocardial infarction and, sudden cardiac death 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.

The use of LHRH agonists may cause a reduction in bone mineral density. In men, preliminary data suggest the use of a bisphosphonate in combination with a LHRH agonist may reduce bone mineral loss.

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

PREGNANCY AND LACTATION

ZOLACOS CP is contraindicated in females and must not be given to pregnant women or nursing mothers.

EFFECT ON ABILITY TO DRIVE AND USE MACHINERY

During treatment with COSUDEX, somnolence has been reported and 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.

ADVERSE EFFECTS**BICALUTAMIDE**

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the 50 mg COSUDEX plus LHRH analogue arm of the pivotal LHRH combination study.

Frequency	System Organ Class	Event
Very common (≥10%)	Blood and Lymphatic	Anaemia
	Nervous System Disorders	Dizziness
	Vascular disorders	Hot flush
	Gastrointestinal disorders	Abdominal pain, constipation, nausea
	Renal and urinary disorders	Haematuria
	Very common (continued)	Reproductive system and breast disorders
	General disorders and administration site conditions	Asthenia, oedema
Common (≥1% and <10%)	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Decreased libido, depression
	Nervous System Disorders	Somnolence
	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported) ^e , Cardiac failure ^e
	Gastrointestinal disorders	Dyspepsia, flatulence,
	Hepatobiliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia ^b
	Skin and subcutaneous tissue disorders	Alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritus
	Reproductive system and breast disorders	Erectile dysfunction
	General disorders and administration site conditions	Chest pain
	Investigations	Weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Hypersensitivity, angioedema, and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease ^c . Fatal outcomes have been reported.
Rare (≥0.01% and <0.1%)	Hepatobiliary disorders	Hepatic failure ^d . Fatal outcomes have been reported.

- ^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 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.
- ^d 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.
- ^e Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when COSUDEX 50 mg was used in combination with LHRH agonists.

GOSERELIN

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

Table 6 ZOLADEX adverse drug reaction by frequency and System Organ Class (SOC)

Frequency Descriptor	SOC	Males
Very Common (≥10%)	Psychiatric disorders	Libido decreased ^a
	Vascular disorders	Hot flush ^a
	Skin and subcutaneous tissue disorders	Hyperhidrosis ^a
	Reproductive system and breast disorders	Erectile dysfunction
Common (≥ 1%-and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired ^b
	Nervous system disorders	Paraesthesia
		Spinal cord compression
	Cardiac disorders	Cardiac failure ^f Myocardial infarction ^f
	Vascular disorders	Blood pressure abnormal ^c
	Skin and subcutaneous tissue disorders	Rash ^d
	Musculoskeletal, connective tissue and bone disorders	Bone pain ^e
	Reproductive system and breast disorders	Gynaecomastia
	General disorders and administration site conditions	Injection site reaction
Investigations	Density decreased, weight increased	
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity
	Musculoskeletal, connective tissue and bone disorders	Arthralgia
	Renal and urinary disorders	Ureteric obstruction

Frequency Descriptor	SOC	Males
	Reproductive system and breast disorders	Breast tenderness
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction
Very rare (<0.01%)	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pituitary tumour
	Endocrine disorders	Pituitary haemorrhage
	Psychiatric disorders	Psychotic disorder
Unknown	Skin and subcutaneous tissue disorders	Alopecia ⁹

- 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.

Reduction in glucose tolerance, manifesting as diabetes or loss of glycaemic control in those with pre-existing diabetes, has been reported during treatment with GnRH agonists including ZOLADEX (see WARNINGS AND PRECAUTIONS).

A small increased risk of developing myocardial infarction and sudden cardiac death has been reported in association with use of GnRH agonists in men.

INTERACTIONS

BICALUTAMIDE

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although *in vitro* studies have suggested the potential for bicalutamide to inhibit cytochrome 3A4, a number of clinical studies show the magnitude of any inhibition is unlikely to be of clinical significance.

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.

Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between COSUDEX 50 mg and LHRH agonists at steady state, COSUDEX

50 mg may prevent the harmful clinical consequences of flare associated with the start of LHRH agonist therapy.

GOSERELIN

None known

OVERDOSAGE

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.

PHARMACEUTICAL PRECAUTIONS

STORAGE CONDITIONS

Store below 25°C.

SHELF LIFE

3 years.

INSTRUCTIONS FOR USE / HANDLING

Goserelin (Zoladex)

Use as directed by the prescriber. Use only if pouch is undamaged. Use immediately after opening pouch.

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 the subcutaneous tissue well away from point of entry and to activate the protective needle sleeve.

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

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

ZolaCos CP is available in two different combinations:

1x ZOLADEX 3.6 mg implant syringe + 28 (1 month) tablets COSUDEX 50 mg

1x ZOLADEX 10.8 mg implant syringe + 84 (3 month) tablets COSUDEX 50 mg

FURTHER INFORMATION

BICALUTAMIDE

Bicalutamide is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction and minor clinical pathology changes, are related to these activities. Enzyme induction and minor cardiac changes seen in dogs have not been observed in man. There are no preclinical findings that preclude the administration of bicalutamide to prostate cancer patients.

List of Excipients

- Lactose monohydrate
- Sodium Starch Glycollate
- Povidone
- Magnesium Stearate
- Hypromellose
- Macrogol 300
- Titanium Dioxide

GOSERELIN

Following long-term repeated dosing with goserelin, an increased incidence of benign pituitary tumours has been observed in male rats. While this finding is similar to that previously noted in this species following surgical castration, any relevance 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 proliferative 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.

ZOLADEX is a synthetically derived peptide.

List of Excipients

- Polyglactin (lactide / glycolide copolymer matrix)

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References

NZ Cosudex Datasheet 190511
NZ Zoladex 3.6 mg Datasheet 010611
NZ Zoladex 10.8 mg Datasheet 010611

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