NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZOLACOS CP 3.6 mg + 50 mg Combination pack
ZOLACOS CP 10.8 mg + 50 mg Combination pack

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

3. PHARMACEUTICAL FORM

Combination pack.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZOLACOS CP is indicated for the treatment of advanced prostate cancer and prevention of disease flare associated with the use of luteinizing-hormone releasing hormone (LHRH) agonists.

4.2 DOSE AND METHOD OF 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).

Method of administration

Goserelin (Zoladex)

For correct administration of ZOLADEX, see instructions on the pouch/carton.

Use as directed by the prescriber. Use extra care when administering ZOLADEX to patients with a low BMI and/or who are receiving full anticoagulation medication (see WARNINGS AND PRECAUTIONS).

Use only if pouch is undamaged. Use immediately after opening pouch.

The following information is intended for medical or healthcare professionals only:

ZOLADEX is administered by subcutaneous injection - read and understand all the instructions fully prior to administration

1. Put the patient in a comfortable position with the upper part of the body slightly raised.
   Prepare the injection site according to the local policy and procedure.

NOTE: Caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches; very thin patients may be at higher risk of vascular injury.

2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light.
   Check that at least part of the ZOLADEX implant is visible. **(Figure 1).**

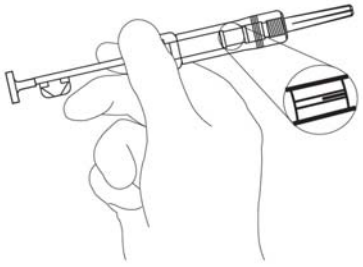

Figure 1.

3. Grasp the plastic safety tab and pull away from the syringe, and discard. **(Figure 2).**
   Remove needle cover. **Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the ZOLADEX implant.**

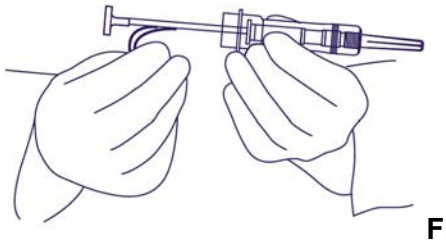

Figure 2.

4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the patient's skin and insert the needle at a slight angle (30 to 45 degrees) to the skin.
With the opening of the needle facing up, **insert needle into the subcutaneous tissue** of the anterior abdominal wall below the navel line, until the protective sleeve touches the patient's skin. **(Figure 3).**

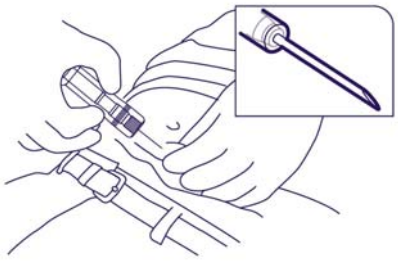

Figure 3.

NOTE: 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 to patients receiving full dose anticoagulation.

5. **Do not penetrate into muscle or peritoneum.** Incorrect grip and angle of presentation is shown **(Figure 4.)**

Figure 4.

6. Depress the plunger **fully**, until you can depress no more, to discharge the ZOLADEX implant and to activate the protective sleeve. You may hear a 'click' and will feel the protective sleeve automatically begin to slide to cover the needle. If the plunger is not depressed fully, the protective sleeve will **NOT** activate.

   NOTE: The needle does not retract.

7. Holding the syringe as shown in **Figure 5,** withdraw the needle and allow protective sleeve to continue to slide and cover needle.
   1. Dispose of the syringe in an approved sharps collector.

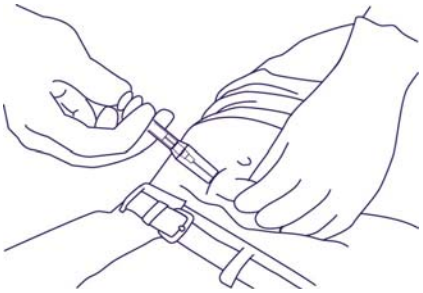

Figure 5.

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

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.

4.3 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 excipients of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Androgen deprivation therapy may prolong the QT interval, although a causal association has not been established with ZOLACOS CP. In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de Pointes prior to initiating ZOLACOS CP.

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 section 4.8). COSUDEX therapy should be discontinued if changes are severe.

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 use adequate contraception methods during and for 130 days after COSUDEX therapy.

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 sections 4.5 and 4.8).

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ZOLACOS CP with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de Pointes should be carefully evaluated (see WARNINGS AND PRECAUTIONS).

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. 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 concomitantly receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see sections 4.4 and 4.8).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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

Breast-feeding

ZOLACOS CP is contraindicated during breast-feeding.

Fertility

Reversible impairment of male fertility has been observed in animal studies with COSUDEX (see section 5.3). A period of subfertility or infertility should be assumed in man.

4.7 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.

4.8 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	Gynaecomastia and breast tenderness[a]
	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.
	Skin and 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] 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.

Increased PT/INR: Accounts of coumarin anticoagulants interacting with COSUDEX have been reported in post marketing surveillance (see sections 4.4. and 4.5).

Goserelin

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

Frequency Descriptor	SOC	Males
Very Common ~~(~~≥10%~~)~~	Psychiatric disorders	Libido decreased[a]
	Vascular disorders	Hot flush[a]
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a],acne[h]
	Reproductive system and breast disorders	Erectile dysfunction
Common (≥ 1% ~~and~~ <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired[b]
	Psychiatric disorders	Mood swings
	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
	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

Frequency Descriptor	SOC	Males
	Endocrine disorders	Pituitary haemorrhage
	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 pharmacoepidemiology 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.
h In most cases acne was reported within one month after the start of ZOLADEX.

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 section 4.4).

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

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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)^{6}Azgly^{10} 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.

5.2 PHARMACOKINETIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

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. Atrophy of seminiferous tubules of the testes is a predicted class effect with anti-androgens and has been observed for all species examined. Reversal of testicular atrophy occurred 4 months after the completion of dosing in a 6-month rat study (at doses of approximately 1.5 or 0.6 times human therapeutic concentrations at the recommended dose of 50 mg or 150 mg, respectively). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 2 or 0.9 times human concentrations at the recommended human dose of 50 mg or 150 mg, respectively). Following 12-months of repeated dosing in dogs (at doses of approximately 7 or 3 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), the incidence of testicular atrophy was the same in dosed and control dogs after a 6 month recovery period. In a fertility study (at doses of approximately 1.5 or 0.6 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), male rats had an increased time to successful mating immediately after 11 weeks of dosing; reversal was observed after 7 weeks off-dose.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Cosudex

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

Zoladex

- Polyglactin (lactide / glycolide copolymer matrix)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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 (not marketed in New Zealand)

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AstraZeneca Limited
P299 Private Bag 92175
Auckland 1142
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

2 April 2009

10. DATE OF REVISION OF TEXT

1 August 2017

References

NZ Cosudex Datasheet 310717
NZ Zoladex 3.6 mg Datasheet 170815
NZ Zoladex 10.8 mg Datasheet 170815

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	SPC style format changes.
4.4, 4.5 & 4.8	New information added regarding potentiation of coumarin when taken with Cosudex.
4.6	Subheadings added. Information added regarding male fertility and Cosudex
5.3	Information added corresponding with new text in 4.6 regarding male fertility - Cosudex.