

AUSTRALIAN PRODUCT INFORMATION

ZOLADEX[®] **goserelin 10.8mg implant**

1 NAME OF THE MEDICINE

Goserelin acetate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZOLADEX SAFESYSTEM[®] Implant contains goserelin 10.8 mg (as goserelin acetate).

For the full list of excipients, see Section [6.1 List of excipients](#).

3 PHARMACEUTICAL FORM

A sterile white to cream coloured cylindrical sustained release implant in which goserelin acetate is dispersed in a polyglactin co-polymer biodegradable matrix.

The implant 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prostate cancer

Palliative treatment of metastatic (M+) or locally advanced prostate cancer where suitable for hormonal manipulation.

Adjuvant and neoadjuvant therapy in combination with radiotherapy for the management of locally advanced prostate cancer in men suitable for hormonal manipulation.

Breast cancer

Management of oestrogen-receptor (ER) positive early and advanced breast cancer in pre and peri menopausal women.

4.2 DOSE AND METHOD OF ADMINISTRATION

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).

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 The plunger should not be withdrawn once the needle is in position.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 ZOLADEX, see instructions on the administration card.

Do not omit or delay injections, as serum testosterone or serum oestradiol levels may rise in males and females respectively.

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

Prostate cancer

One implant of ZOLADEX 10.8 mg injected subcutaneously into the anterior abdominal wall, every 3 months (see Section 5.1 Pharmacological properties).

Adjuvant and/or neoadjuvant ZOLADEX therapy in combination with radiotherapy may include short-term use of an anti-androgen to prevent flare (see Section 5.1 Pharmacodynamic properties Clinical Trials - Adjuvant and neoadjuvant ZOLADEX therapy in combination with radiotherapy section).

Breast cancer

One implant of ZOLADEX 10.8 mg injected subcutaneously into the anterior abdominal wall, every 12 weeks.

Special patient populations

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Use in the elderly

No dosage adjustment is necessary in the elderly.

Paediatric use

ZOLADEX 10.8 mg implant is not indicated for use in children.

4.3 CONTRAINDICATIONS

ZOLADEX is contraindicated in patients with known hypersensitivity to Luteinising Hormone Releasing Hormone (LHRH), LHRH agonist analogues or any of the components of ZOLADEX.

Pregnancy and lactation (see Section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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).

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

Advanced or metastatic breast or prostate cancer

Initially, ZOLADEX, like other LHRH agonists, transiently increases serum testosterone in males and serum oestradiol in females. Although not necessarily associated, there have been reports of temporary increase in bone pain in patients with advanced cancer and bony metastases. These events may last up to two weeks and may need to be managed symptomatically. Some patients may experience a temporary increase in tumour signs and symptoms, which can be managed symptomatically. Rarely, patients with bony metastases have developed hypercalcaemia on initiation of therapy.

For prostate cancer, the use of ZOLADEX in patients with metastatic cancer who are 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 of short-term worsening of these signs and symptoms have been reported during the initial four weeks of ZOLADEX therapy. Consideration should be given to antiandrogen therapy at the start of ZOLADEX therapy since this has been reported to prevent the possible sequelae of the initial rise in serum testosterone.

Hyperglycaemia and diabetes

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving Gonadotrophin Releasing Hormone (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.

Bone mineral density

The use of ZOLADEX causes loss of bone mineral density (BMD). Currently available data suggest that recovery of bone loss occurs after cessation of therapy.

Following two years treatment with ZOLADEX (3.6 mg every 28 days) for early breast cancer, the average loss of bone mineral density was 6.2% and 11.5% at the femoral neck and lumbar spine respectively. This loss has been shown to be partially reversible at the one year off treatment follow-up with recovery to 3.4% and 6.4% below baseline at the femoral neck and lumbar spine

respectively.

Particular care should be taken in assessing patients for treatment if they exhibit risk factors for osteoporosis such as family history, slight build, heavy smoking and low dietary calcium intake or in women with chronic anovulatory menstrual disturbances, patients treated with glucocorticoids, or chronically immobilised. Patients with significant risk factors should have bone density measured before commencing treatment. The clinician should discuss relevant risk factors with patients on an individual basis.

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 (see Section [4.5 Interactions with other medicines and other forms of interactions](#)).

Vaginal bleeding

During early treatment with goserelin acetate some women may experience vaginal bleeding of variable duration and intensity. Such bleeding probably represents oestrogen withdrawal bleeding and is expected to stop spontaneously. If bleeding continues, the reason should be investigated.

During treatment with LHRH analogues patients may enter the natural menopause. Rarely, menstruation does not resume on cessation of ZOLADEX therapy.

Use in the elderly

See Section [4.2 Dose and method of administration](#).

Paediatric use

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

No data available.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ZOLADEX 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

The expected pharmacology of ZOLADEX 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 24 times the recommended human dose based on AUC).

Use in Pregnancy – Category D (see Section 4.3 Contraindications)

ZOLADEX should not be used in pregnancy as there is a theoretical risk of pregnancy loss or fetal abnormality if LHRH agonists are used during pregnancy. A pregnancy test should be performed prior to administering the ZOLADEX implant in patients who could become pregnant.

Patients who could become pregnant should use non-hormonal contraceptive methods during treatment with ZOLADEX and until resumption of menstruation following discontinuation of treatment with ZOLADEX. Time to return of menses after cessation of therapy with ZOLADEX may be prolonged in some patients.

Use in Lactation (see Section 4.3 Contraindications)

The use of ZOLADEX during breast feeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that ZOLADEX 10.8 mg results in impairment of ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Table 1 ZOLADEX adverse drug reactions (clinical trials and post-marketing)

Frequency	System Organ Class	Event (Males)	Event (Females)
Very common (≥10%)	Psychiatric disorders	Libido decreased ^a	Libido decreased ^a
	Vascular disorders	Hot flush ^a , blood pressure abnormal ^b	Hot flush ^a
	Skin and subcutaneous tissue disorders	Hyperhidrosis ^a	Hyperhidrosis ^a , acne ^h

Frequency	System Organ Class	Event (Males)	Event (Females)
	Reproductive system and breast disorders	Erectile dysfunction, gynaecomastia, breast tenderness	Vulvovaginal dryness, breast enlargement
	Nervous system disorders	Paraesthesia	(see Common)
	General disorders and administration site conditions	(see Common)	Injection site reactions
	Investigations	Bone density decreased	(see Common)
Common (≥1% and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired ^c	(see Unknown)
	Psychiatric disorders	Mood swings	Mood altered, depression
	Nervous system disorders	Spinal cord compression	Paraesthesia, headache
	Vascular disorders	(see Very common)	Blood pressure abnormal ^b
	Renal and urinary tract disorder	Incontinence and urinary frequency (after radiotherapy)	N/A
	Skin and subcutaneous tissue disorders	Rash ^d	Rash ^d , alopecia ⁱ
	Musculoskeletal, connective tissue and bone disorders	Bone pain ^e , arthralgia	Arthralgia
	General disorders and administration site conditions	Injection site reaction	Tumour flare, tumour pain
	Cardiac disorders	Cardiac failure ^f , myocardial infarction ^f	(see Unknown)
	Investigations	Weight increased	Bone density decreased, weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity	Drug hypersensitivity
	Renal and urinary tract disorders	Ureteric obstruction	N/A
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction	Anaphylactic reaction
	Reproductive system and breast disorders	N/A	Ovarian cyst
	Endocrine disorders	Pituitary haemorrhage/Infarction	(see Very rare)
Very rare (<0.01%)	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pituitary tumour	Pituitary tumour
	Endocrine disorders	(see Rare)	Pituitary haemorrhage/infarction
	Psychiatric disorders	Psychotic disorder	Psychotic disorder
Unknown	Skin and subcutaneous tissue disorders	Alopecia ^g	(see Common)
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N/A	Degeneration of uterine fibroid
	Metabolism and nutrition disorders	(see Common)	Glucose tolerance impaired ^c
	Cardiac disorders	(see Common)	Cardiac failure ^f , myocardial infarction ^f

^a These are pharmacological effects which seldom require withdrawal of therapy.

^b 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.

- ^c 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.
- ^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.
- ^h In most cases acne was reported within one month after the start of ZOLADEX.
- ⁱ Loss of head hair has been reported in females, including younger patients treated for benign conditions. This is usually mild but occasionally can be severe.

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

There is limited experience of overdosage in humans. In cases where ZOLADEX 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 ZOLADEX. If overdosage occurs, this should be managed symptomatically.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Goserelin acetate is a GnRH agonist (also known as LHRH agonist).

Goserelin acetate is a potent synthetic decapeptide analogue of LHRH. When given acutely, goserelin acetate will release luteinising hormone (LH) from the pituitary gland. However, following chronic administration, goserelin acetate is a potent inhibitor of gonadotrophin production resulting in gonadal suppression and consequently sex organ regression.

In animals and humans, following an initial stimulation of pituitary LH secretion and a transient elevation in serum testosterone in males, or serum oestradiol in females, chronic administration results in inhibition of gonadotrophin secretion. The result is a sustained suppression of pituitary LH occurring within approximately 3 weeks after initiation of therapy. This suppression of gonadal hormones is then maintained as long as therapy is continued.

In men, by around 21 days after the first implant injection, testosterone concentrations have decreased to within the castrate range and remain suppressed with treatment every 3 months. If in exceptional circumstances repeat dosing does not occur at 3 months, data indicate that castrate levels of testosterone are maintained for up to 16 weeks in the majority of patients.

In women, serum oestradiol concentrations are suppressed by around 4 weeks after the first implant injection and remain suppressed until the end of the treatment period at levels comparable with

those observed in postmenopausal women. Suppression of oestradiol is associated with a response in hormone-dependent breast cancer in premenopausal women and will result in amenorrhoea in the majority of patients.

Clinical trials

Prostate cancer - Adjuvant and neoadjuvant ZOLADEX therapy in combination with radiotherapy

Five phase III, open-labelled, randomised, controlled, multi-centred clinical trials have been conducted to evaluate the added value of adjuvant and/or neoadjuvant ZOLADEX therapy in combination with radiotherapy in patients with histologically proven prostate cancer. The majority of patients had locally advanced disease (T2 N+, T3 or T4, N0/Nx, M0). All studies have been performed by three independent collaborative oncology groups (European Organisation for Research and Treatment of Cancer [EORTC], the Radiation Therapy Oncology Group [RTOG]) and the Trans-Tasman Radiation Oncology Group [TROG]), and have reported results from median follow-up of more than 5 years. Table 2 summarises the study design, patient populations and median follow-up periods for these studies.

Table 2 Study design, patient population and median follow-up period for adjuvant and/or neo-adjuvant ZOLADEX combined with radiotherapy clinical trials

	Adjuvant		Neo-adjuvant	Neo and adjuvant	
Trial	RTOG 85-31 (n=945)	EORTC 22863 (n=415)	RTOG 86-10 (n=456)	RTOG 92-02 (n=1514)	TROG 96-01 [^] (n=818)
Treatment	ZOLADEX* + RT	ZOLADEX* [#] + RT	ZOLADEX* [§] + RT	ZOLADEX* [§] + RT	ZOLADEX* [§] + RT
Comparator	RT alone + ZOLADEX at relapse	RT alone	RT alone	ZOLADEX* [§] + (neo) only RT	RT alone
Duration	Last week of RT continued indefinitely	Day 1 of RT continued for 3 years post RT	2 months prior to & during RT	2 months prior to, during & 2 years post RT (treatment) 2 months prior to & during RT (comparator)	2 and 5 months prior neoadjuvant and 1 month during RT
Patient population	T1-2, N+ & T3 (any N); Lesions <25 cm ³ ; prior prostatectomy allowed [^]	T1-2, N0-X (G3) & T3 - 4N0 (any G)	T2b-4, M0; N+ allowed [^] ; Lesions ≥25cm ³	T2c-T4; PSA < 150 ng/mL; N+ allowed [^] ; KS≥70	T2b-4, N0/NX M0
Median follow-up	7.6 years ^a	5.5 years ^b	6.7 years ^c	5.8 years ^d	5.9 years ^e

T, N – Tumour, node in accordance with the UICC classification; G – WHO grade; *3.6 mg s.c every 4 weeks; [#] plus 1 month of oral cyproterone acetate 150 mg/day initiated 1 week prior to ZOLADEX to prevent flare; RT - radiotherapy; [§] combined with oral flutamide (250 mg three times daily); [^] if penetration to the margins of resection and/or seminal vesicle involvement + Karnofsky performance status >60%; [^] if below the common iliac chain; KS – Karnofsky score.

^a Pilepich et al 2003a, Proc Am Soc Oncol 22: 1530 (including ASCO presentation slides), and Pilepich et al 2003b, Int J Radiation Oncol Biol Phys 57: S172-3

^b Bolla et al 2002, Lancet 360: 103-8

^c Pilepich et al 2001, Int J Radiation Oncol Biol Phys 50: 1243-1252 and Shipley et al 2002, Int J Radiation Oncol Biol Phys 54: 1302-1310

^d Hanks et al 2003, JCO 21: 3972-3978

^e Denham et al 2005, Lancet Oncology 2005; 841-50

Adjuvant ZOLADEX therapy long-term (≥ 3 years) significantly improved disease-free survival and overall survival compared to radiotherapy alone (Table 3 and Table 4). Neoadjuvant ZOLADEX therapy for two months prior and during radiotherapy significantly improved disease-free survival but not overall survival compared to radiotherapy alone (Table 5). A combination of neoadjuvant and adjuvant ZOLADEX therapy with radiotherapy also significantly improved disease-free survival but not overall survival compared to neoadjuvant ZOLADEX with radiotherapy (Table 6) and radiotherapy alone (Table 7). There was no significant difference in disease-free survival between 3 months and 6 months neoadjuvant plus adjuvant ZOLADEX (Table 7).

Table 3 Adjuvant ZOLADEX efficacy results for RTOG 85-31 (median follow-up: all patients 7.6 years; alive patients 10 years)

Endpoint	10 year estimates (%)		p value
	ZOLADEX+RT	RT alone	
Overall survival	47*	38	0.0043
Disease-free survival	30	9	<0.0001

*ASCO presentation slides

Table 4 Adjuvant ZOLADEX efficacy results for EORTC 22863 (median follow-up: all patients 5.5 years)

Endpoint	5 year estimates (%)		Hazard ratio [95% CI]
	ZOLADEX+RT	RT alone	
Overall survival	78	62	0.51 [0.36-0.73]
Disease-free survival	74	40	0.34 [0.26-0.46]

CI – confidence interval

Table 5 Neoadjuvant ZOLADEX efficacy results for RTOG 86-10 (median follow-up: all patients 6.7 years; alive patients 8.6 years)

Endpoint	8 year estimates (%)		p value
	ZOLADEX+RT	RT alone	
Overall survival	53 {53*}	44 {43*}	0.10 {0.08*}
Disease-free survival	49	34	0.004

*updated analyses (Shipley et al 2002 – all patients 6.7 years; alive patients 9.0 years)

Table 6 Neoadjuvant and/or adjuvant ZOLADEX efficacy results for the total RTOG 92-02 population (median follow-up: all patients 5.8 years; alive patients 6.3 years)

Endpoint	5 year estimates (%)		p value
	Neo & adjuvant ZOLADEX	Neo ZOLADEX only	
Overall survival	80.0	78.5	ns
Disease-free survival	46	28	< 0.0001

ns – not significant

Table 7 **Neoadjuvant and/or adjuvant ZOLADEX efficacy results for the total TROG 96.01 population (median follow-up: all patients 5.9 years)**

Endpoint	5 year estimates (%)			
	Neo ZOLADEX (3 months)	Neo ZOLADEX (6 months)	RT alone	Hazard ratio [95% CI]
Overall survival	N/A ^d	N/A ^d	N/A ^d	N/A ^d
Disease-free survival	49.0	52.0	32.0	0.65 [0.52-0.80] ^a 0.56 [0.45-0.69] ^b 0.85 [0.67-1.07] ^c

ns – not significant

^a RT alone vs. 3 months

^b RT alone vs. 6 months

^c 6 months vs. 3 months

^d Results for overall survival (defined as death from any cause) was not presented.

Breast cancer

Premenopausal women with locally advanced or metastatic oestrogen receptor-positive breast cancer Study D8666C00001

A Phase III, open-label, randomised, parallel group, multicentre trial was conducted in premenopausal women aged ≥ 20 years with histologically/cytologically confirmed locally advanced or metastatic ER-positive breast cancer, who were candidates to receive endocrine therapy (Study D8666C00001). Patients were randomised to receive either ZOLADEX 3.6 mg subcutaneous implant once every 4 weeks for 24 weeks or ZOLADEX 10.8 mg subcutaneous implant once every 12 weeks for 24 weeks. All patients also received a daily oral dose of tamoxifen (20 mg). Premenopausal status was defined as experiencing menses within 1 year prior to randomisation, and serum concentrations for oestradiol ≥ 36.71 pmol/L and follicle-stimulating hormone (FSH) ≤ 30 IU/L within 4 weeks prior to randomisation (for patients who had undergone a hysterectomy, only the latter criterion was required). A total of 222 patients were randomised into the study; 109 patients in the ZOLADEX 10.8 mg group, 113 patients in the ZOLADEX 3.6 mg group. Most of the patients (74.3% in the 10.8 mg group, 73.5% in the 3.6 mg group) had tumours classified as invasive ductal. All patients were ER-positive, and the majority of patients were both ER- and progesterone receptor (PgR)-positive [82.6% (n = 90) in the ZOLADEX 10.8 mg group; 77.9% (n = 88) in the ZOLADEX 3.6 mg group]. Median age was 42.0 years (range: 23, 54). Patient ethnicities were Japanese (26.6%) or non-Japanese Asian (73.4%). The most common countries of residence were Japan (26.6%), India (25.3%), and Philippines (19.8%).

The primary endpoint of the study was progression-free survival (PFS) at week 24. In total, 61.5% (n = 67) of patients in the ZOLADEX 10.8 mg group and 60.2% (n = 68) of patients in the ZOLADEX 3.6 mg group were progression free at 24 weeks (treatment difference: 1.3; 95% CI -11.4, 13.9; Table 8). The lower bound of the 95% CI was above the pre-defined margin of -17.5%, and therefore ZOLADEX 10.8 mg met the criteria for non-inferiority compared with ZOLADEX 3.6 mg.

Table 8 Progression-free survival at week 24 in Study D8666C00001 (FAS)

	Study D8666C00001	
	ZOLADEX 10.8 mg (N=109)	ZOLADEX 3.6 mg (N=113)
Patients with PFS at week 24, n (%)	67 (61.5)	68 (60.2)
Difference in % (ZOLADEX 10.8 mg- ZOLADEX 3.6 mg) [95% CI]	1.29 [-11.4 to 13.9]	

CI= confidence interval; FAS= full analysis set; PFS= progression-free survival.

A secondary objective of the study was oestradiol serum concentrations (blood collected prior to ZOLADEX administration) at 24 weeks. After adjusting for treatment group, baseline oestradiol serum concentrations and ethnicity (Japanese vs non-Japanese) as covariates, the ratio of the least square means of oestradiol concentrations for the 10.8 mg group compared to the 3.6 mg group at 24 weeks was 0.92 (95% CI 0.74, 1.14). Unadjusted mean serum oestradiol concentrations were similar in the ZOLADEX 10.8 mg and ZOLADEX 3.6 mg groups at week 12 (96.5 pmol/L and 93.2 pmol/L, respectively) and at week 24 (74.5 pmol/L and 91.0 pmol/L, respectively).

Study D8664C00008

In a Phase III, open-label, randomised, multicentre study in 98 premenopausal women with ER-positive advanced breast cancer, ZOLADEX 10.8 mg every 12 weeks plus tamoxifen 20 mg daily was compared to ZOLADEX 3.6 mg every 4 weeks plus tamoxifen. Patients in this trial were Japanese (39.8%) or Caucasian (60.2%). Median age was 43.0 years (range: 26, 59). Recruitment ended early due to changes in treatment practice; 98 of 260 planned patients were randomised, and the study was underpowered to formally demonstrate non-inferiority for PFS at Week 24. PFS at Week 24 was 69.4% with ZOLADEX 10.8 mg and 73.5% with ZOLADEX 3.6 mg (treatment difference -4.1%; 95% CI: -21.4, 13.6). Mean serum oestradiol concentrations at Week 24 were 7.24 pmol/L in the 10.8 mg group vs 10.36 pmol/L in the 3.6 mg group. After adjusting for treatment group and baseline oestradiol serum concentrations as covariates, the ratio of the least square means of oestradiol concentrations for the 10.8 mg group compared to the 3.6 mg group at 24 weeks was 0.93 (95% CI 0.60, 1.46).

Premenopausal women with oestrogen receptor-positive early breast cancer

Study D8664C00004

A Phase II, open-label, randomised, parallel group, multicentre study was conducted to compare oestradiol suppression between ZOLADEX 10.8 mg given once every 12 weeks and ZOLADEX 3.6 mg given once every 4 weeks in premenopausal patients with ER-positive early breast cancer (Study D8664C00004). All patients also received concomitant oral tamoxifen (20 mg daily). One hundred and seventy patients were randomised into the study; 86 patients to the ZOLADEX 10.8 mg group and 84 patients to the ZOLADEX 3.6 mg group. Most patients had invasive breast cancer (95.3%) that was PgR-positive (94.7%), and stage T1 (60.6%). All patients were Japanese. Median age was 44.0 years (range: 26, 53).

The primary objective for this study was to examine whether ZOLADEX 10.8 mg depot was non-inferior to ZOLADEX 3.6 mg by assessment of AUC of oestradiol concentration from week 4 to week 24 of treatment.

The geometric mean of oestradiol AUC_{4-24 week} was 67.25 pmol/L per week in the ZOLADEX 10.8 mg group and 69.56 pmol/L per week in the ZOLADEX 3.6 mg group. The AUC ratio of the ZOLADEX 10.8 mg/ZOLADEX 3.6 mg group, adjusted by baseline oestradiol value, was 0.974 (95% CI: 0.799 to 1.188). The 95% CI upper limit was below the predefined non-inferiority margin of 1.25, indicating that ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg in terms of

oestradiol suppression in premenopausal women with ER-positive breast cancer.

After week 4, the mean oestradiol serum concentrations were maintained below 110 pmol/L in most patients ($\geq 98.8\%$) in both the ZOLADEX 10.8 mg and ZOLADEX 3.6 mg groups, i.e. within a post-menopausal range. Most of the patients (98.2%) in both treatment groups had no menstruation after week 8. Mean FSH serum concentrations after week 4 in the range of 1.283 IU/L to 2.117 IU/L in both treatment groups.

5.2 PHARMACOKINETIC PROPERTIES

Goserelin acetate has a serum elimination half-life of approximately 4.2 hours in subjects with normal renal function compared to 13 minutes for natural LHRH.

Although the half-life is increased in patients with impaired renal function, absolute clearance is still relatively rapid. The existence of a non-renal, presumably hepatic, clearance and the absence of an increased incidence of possible adverse reactions in such patients imply that no adjustment in the proposed dosage regimen is necessary in patients with renal impairment.

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

The implant formulation of the drug is dispersed in a cylindrical rod of a biodegradable and biocompatible polyglactins and is released continuously when injected subcutaneously. The implant is supplied in a purpose-designed applicator with 14-gauge needle.

Administration of ZOLADEX 10.8 mg, in accordance with the dosage recommendations, ensures that exposure to goserelin is maintained with no clinically significant accumulation. The peak serum concentrations occur during the first 24 hours post administration. In studies of prostate cancer patients, the mean serum concentration at 2 hours post administration is 8.6 ± 2.9 (SD) ng/mL with an inter-individual range of up to 11-fold.

Mean systemic clearance values for goserelin were about 100 to 200 mL/min with an inter-individual range of up to 6-fold.

Serum goserelin concentrations become low by end of the dosing interval; delaying or omitting scheduled doses should be avoided as it may lead to increased testosterone or oestradiol levels and loss of efficacy in prostate or breast cancer patients, respectively.

5.3 PRECLINICAL SAFETY DATA

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 1.8 times the recommended 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 $\mu\text{g/kg/day}$ (approximately 9 to 18 times the recommended 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

ZOLADEx 10.8 mg SAFESYSTEM 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

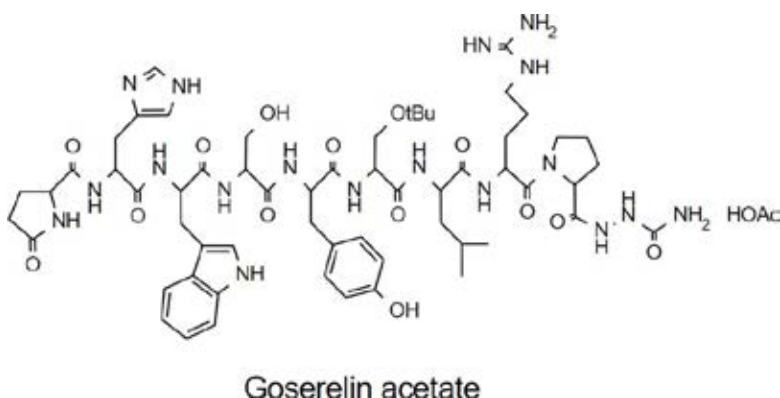
ZOLADEX 10.8 mg SAFESYSTEM Implant is supplied as a sterile, biodegradable cylindrical implant containing the equivalent of 10.8 mg of goserelin base together with the inactive ingredient polyglactin and is presented as 1x (one) pre-filled syringe applicator for subcutaneous injection per carton.

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



Molecular Formula: C₅₉H₈₄N₁₈O₁₄ (base)

Molecular Weight: 1269 (base)

CAS number

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

22 May 1996

10 DATE OF REVISION

(draft 21 August 2026)

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2	New indication, dosing recommendation and clinical trial information (efficacy and safety information) for breast cancer and revision to prostate cancer information
4.6, 5.3	Update to preclinical information
Various	Editorial changes

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