ZOLADEX 10.8 mg IMPLANT

goserelin

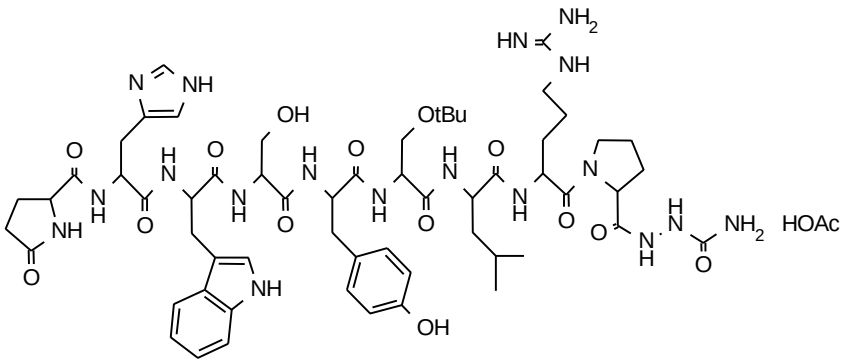
PRODUCT INFORMATION

NAME OF THE MEDICINE

Goserelin acetate. It is a Gonadotrophin Releasing Hormone Agonist (GnRH Agonist) - [also known as Luteinising Hormone Releasing Hormone Agonist (LHRH Agonist)].

Chemical Structure:

Structural Formula:



Goserelin acetate

CAS Registry Number: 65807-02-5 (Goserelin base)

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

Molecular Weight: 1269 (base)

DESCRIPTION

ZOLADEX 10.8 mg SafeSystem™ Implant contains goserelin acetate in an amount equivalent to 10.8 mg of goserelin base.

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.

PHARMACOLOGY

Goserelin acetate is a potent synthetic decapeptide analogue of luteinising hormone releasing hormone (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, 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, and a reduction in serum testosterone levels in males to a range normally seen in surgically castrated men. This suppression is then maintained as long as therapy is continued. 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.

Pharmacokinetics

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. 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 levels and loss of efficacy.

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 1 summarises the study design, patient populations and median follow-up periods for these studies

Table 1 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[δ]; Lesions ≥25cm^3	T2c-T4; PSA < 150 ng/mL: N+ allowed[δ]; 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%; δ 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 (Tables 2 and 3). Neoadjuvant ZOLADEX therapy for two months prior and during radiotherapy significantly improved disease-free survival but not overall survival compared to radiotherapy alone (Table 4). 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 5) and radiotherapy alone (Table 6). There was no significant difference in disease-free survival between 3 months and 6 months neoadjuvant plus adjuvant ZOLADEX (Table 6).

Table 2 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 3 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 4 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 5 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 6 Neoadjuvant and/or adjuvant ZOLADEX efficacy results for the total TROG 96.01 population (median follow-up: all patients 5.9 years)

	5 year estimates (%)			
Endpoint	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.

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.

CONTRAINDICATIONS

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

PRECAUTIONS

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 **DOSAGE AND ADMINISTRATION**).

ZOLADEX 10.8 mg is not indicated for use in females, since there is insufficient evidence of reliable suppression of serum oestradiol. For female patients requiring treatment with goserelin, refer to the prescribing information for ZOLADEX 3.6 mg.

ZOLADEX 10.8 mg is not indicated for use in children as safety and efficacy have not been established in this group of patients.

Initially ZOLADEX, like other GnRH agonists, transiently increases serum testosterone. 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.

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.

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

ZOLADEX causes loss of bone mineral density.

Hyperglycaemia and Diabetes

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.

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.

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.

Carcinogenicity / mutagenicity

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.

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

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.

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 57 times the recommended monthly dose for a human based on AUC).

Use in Pregnancy

ZOLADEX 10.8 mg is not indicated for use in females.

Use in Lactation

ZOLADEX 10.8 mg is not indicated for use in females.

ADVERSE EFFECTS

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

Frequency	System Order Class	Event (Males)
Very Common (≥10%)	Psychiatric disorders	Libido decreased[a]
	Vascular disorders	Hot flush[a], blood pressure abnormal[b]

Frequency	System Order Class	Event (Males)
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a]
	Reproductive system and breast disorders	Erectile dysfunction, gynaecomastia, breast tenderness
	Nervous system disorders	Paraesthesia
	Investigations	Bone density decreased
Common (≥ 1% and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired[c]
	Nervous system disorders	Spinal cord compression
	Renal and urinary tract disorder	Incontinence and urinary frequency (after radiotherapy)
	Skin and subcutaneous tissue disorders	Rash[d]
	Musculoskeletal, connective tissue and bone disorders	Bone pain[e], arthralgia
	General disorders and administration site conditions	Injection site reaction
	Cardiac disorders	Cardiac failure[f], myocardial infarction[f]
	Investigations	Weight increased
	Psychiatric disorders	Mood swings
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity
	Renal and urinary 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 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.

DOSAGE AND 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.

Use extra care when administering ZOLADEX to patients with a low BMI and/or who are receiving full anticoagulation medication (see **PRECAUTIONS**).

Adult Men (including the elderly)

One implant of ZOLADEX 10.8 mg injected subcutaneously into the anterior abdominal wall, every 3 months (see **PHARMACOLOGY**). 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.

Adjuvant and/or neoadjuvant ZOLADEX therapy in combination with radiotherapy may include short-term use of an anti-androgen to prevent flare (see **CLINICAL TRIALS - Adjuvant and neoadjuvant ZOLADEX therapy in combination with radiotherapy section**).

Adult Women

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

Children

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

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

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

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

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.

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4

NAME AND ADDRESS OF SPONSOR

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DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22nd May 1996

DATE OF MOST RECENT AMENDMENT

16th May 2017