ZOLADEX 3.6 mg IMPLANT

goserelin

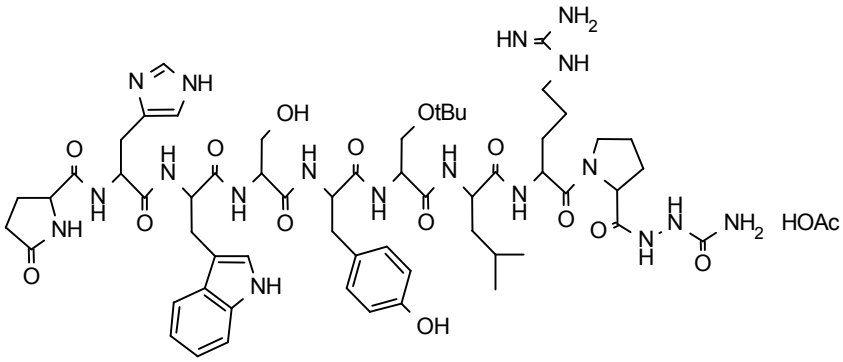
PRODUCT INFORMATION

NAME OF THE DRUG

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 SafeSystem™ Implant contains goserelin acetate in an amount equivalent to 3.6 mg of goserelin base.

A sterile white to cream coloured cylindrical implant in which goserelin acetate is dispersed in a cylindrical lactide/glycolide co-polymer rod of a biodegradable and biocompatible matrix.

The implant is released continuously over at least 28 days when injected subcutaneously.

The implant is supplied in a purpose-designed single dose syringe applicator with 16-gauge needle. 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 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 3 weeks after initiation of therapy. This suppression of hormones in both men and women is then maintained as long as treatment is continued. 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.

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 every 28 days. This inhibition leads to prostate tumour regression and symptomatic improvement in the majority of patients.

In women serum oestradiol concentrations are suppressed by around 21 days after the first implant injection and, with continuous treatment every 28 days, remain suppressed at levels comparable with those observed in postmenopausal women. This suppression is associated with endometrial thinning, suppression of follicular development within the ovary and a response in hormone dependent breast cancer (tumours that are ER-positive and/or PgR-positive), endometriosis and uterine fibroids and will result in amenorrhoea in the majority of patients.

During treatment with a LHRH agonist patients may enter the natural menopause. Rarely, some women do not resume menses on cessation of therapy.

Pharmacokinetics

Although bioavailability from the implant may be variable, the formulation releases the drug at effective concentrations to sustain a biological response for at least 28 days.

Goserelin acetate has a serum elimination half-life of approximately 4.2 hours in male subjects with normal renal function compared to 13 minutes for natural LHRH. ZOLADEX is poorly protein bound (20–28%).

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 impairment.

ZOLADEX Implant releases goserelin acetate continuously with peak serum concentrations occurring approximately 2 weeks after administration with inter-individual differences in these peak concentrations (1.76±0.52 ng per mL to 5.04±0.71 ng per mL).

Serum goserelin concentrations become low by day 28; delaying or omitting scheduled doses should be avoided.

There is no evidence of drug accumulation when ZOLADEX Implant is administered at 4 weekly intervals.

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.

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 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	T1-2N+ & T3 (any N); Lesions <25 cm^3 ; prior prostatectomy allowed ^	T1-2N0-X (G3) & T3 - 4N0 (any G)	T2b-4M0; N+ allowed[δ]; Lesions ≥25 cm^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

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]

[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.

Adjuvant therapy in early breast cancer

Several clinical trials, each open and randomised, were evaluated to assess the efficacy and safety of long-term adjuvant ZOLADEX therapy in the standard of care for pre-/perimenopausal women in early breast cancer (see Table 7). All trials were conducted by independent collaborative oncology groups, and the protocolled duration of ZOLADEX treatment, administered at four weekly intervals, varied from 2 years to 5 years. The key efficacy end-points in both the pivotal and supportive trials were disease-free survival and overall survival. The ZIPP trials were designed to allow data to be pooled.

Table 7

Trial	**Treatment regimen**	**Patient population**
ZEBRA 118630/2802 (n=1640)	ZOLADEX 3.6 mg for 2 years· Six 28-day cycles of CMF	Pre-/perimenopausal (<50 yrs) with node positive, stage II disease. 74% and 19% of patients were ER-positive and ER-negative, respectively in the primary efficacy population.
INT0101 (n=1537)	Six 28-day cycles of CAF CAF followed by ZOLADEX 3.6 mg for 5 yrs CAF followed by ZOLADEX 3.6 mg + tamoxifen for 5 yrs	Premenopausal with receptor positive, node positive early breast cancer. 99.6% of patients were ER and/or PgR-positive.
ZIPP trials (n=2659)	Std therapy[a] plus ZOLADEX 3.6 mg for 2 yrs Std therapy[a]	Pre-/perimenopausal and/or aged <50 yrs and were treated for operable carcinoma of the breast

[a]standard adjuvant therapy could include radiotherapy and/or chemotherapy and/or tamoxifen; ER Oestrogen receptor; PgR Progesterone receptor; CAF Combination chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil; CMF Combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil; ZIPP ZOLADEX in Premenopausal Patients (combined data analysis of four trials)

Results from the ZEBRA trial

There was a statistically significant interaction between trial treatment and ER status [Hazard ratio=0.54; 95% CI=0.37-0.78; p=0.001]. In a prospective, protocolled sub-group analysis by oestrogen receptor [ER] status, ZOLADEX 3.6 mg was equivalent to CMF in terms of disease-free survival in patients with ER-positive tumours. Analyses of overall survival were comparable, although the confidence intervals were wider. In patients with ER-negative tumours, disease-free survival and overall survival were significantly greater in the CMF group. These results are tabulated below (see Table 8).

The Kaplan-Meier disease-free survival curve for ER-positive patients does not indicate any loss of efficacy 6 years after starting ZOLADEX 3.6 mg therapy (ie 4 years after cessation of therapy).

Table 8 Disease-free survival and overall survival from the ZEBRA trial

Analysis and patient population	Hazard ratio[a]	95% CI	p value	Number of events/patients
Disease-free survival				
ER+ve patients	1.02	0.85-1.22	0.854	477/1154
ER–ve patients	1.83	1.31-2.55	<0.001	144/297
All patients	1.21	1.04-1.40	0.016	669/1560
Overall survival				
ER +ve patients	1.03	0.79-1.35	0.802	222/1154
ER –ve patients	1.89	1.27-2.82	0.001	103/297
All patients	1.23	1.00-1.51	0.055	354/1560

[a]ZOLADEX 3.6 mg/CMF: a hazard ratio <1 favours ZOLADEX 3.6 mg

Bone mineral density (BMD)

Following two years of ZOLADEX 3.6 mg treatment in early breast cancer, the average loss of BMD 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.

Amenorrhoea

Six months after completing the 2 year course of ZOLADEX 3.6 mg therapy, <40% of patients were amenorrhoeic. If patients who were not menstruating normally at trial entry, or had a hysterectomy or had recurrence during the trial (and therefore may have received another amenorrhoea-inducing treatment) are excluded, the number of amenorrhoeic patients 6 months post treatment was <24%. Most of these patients were aged >40 years of age at trial entry.

Safety

Patients receiving ZOLADEX 3.6 mg experienced higher incidences of effects caused by oestrogen suppression (eg hot flushes, vaginal dryness/soreness etc), than patients receiving combination chemotherapy (CMF), but within 6 months of completing therapy, these incidences had decreased to below those seen in CMF patients. Patients who received CMF experienced a higher incidence of the expected side effects of chemotherapy (eg cytopenia, nausea, vomiting and alopecia), than patients who received ZOLADEX 3.6 mg.

Results from the supportive trials

The main disease-free survival and overall survival analyses are tabulated below (see Table 9).

Table 9 Disease-free survival and overall survival analyses

Trial and comparator arms	Patient population	Hazard ratio[a]	95% CI	p value	Number of events/patients
INT 0101 CAF then ZOLADEX 3.6 mg vs CAF	Primary population (all randomised patients)				
Disease-free survival		0.83	0.68-1.02	0.073	385/1021
Overall survival		0.88	0.68-1.14	0.35	236/1021
ZIPP trials Std therapy[b] plus ZOLADEX 3.6 mg vs std therapy[b]	ZIPP efficacy population[c]				
Disease-free survival		0.82	0.71-0.94	0.006	785/2659

Trial and comparator arms	Patient population	Hazard ratio[a]	95% CI	p value	Number of events/patients
Overall survival		0.84	0.69-1.02	0.085	407/2659

[a] a hazard ratio <1 indicates a better result for the first treatment compared to the second treatment. In trial INT0101, recognised important prognostic factors were included in the statistical model and patients with unknown baseline prognostic factor data were excluded from the analyses. Exclusion of these patients did not affect the conclusions of the analyses; [b] Standard adjuvant therapy could include radiotherapy and/or chemotherapy and/or tamoxifen; [c] all randomised patients except those from 1 centre (50 patients) who electively did not receive tamoxifen therapy; CAF Combination chemotherapy with cyclophosphamide, doxorubicin [adriamycin] and 5-fluorouracil; ZIPP ZOLADEX in Premenopausal Patients (combined data analysis)

Overall the efficacy data demonstrates that ZOLADEX 3.6 mg is effective as an alternative to combination chemotherapy, in patients with hormone receptor positive early breast cancer (as demonstrated by the ZEBRA trial). ZOLADEX may also provide additional therapeutic benefit when used after combination chemotherapy (as demonstrated by study INT0101). The clinical evaluation of ZOLADEX is mainly in studies of two years duration when it has been shown to be equivalent to chemotherapy. Studies up to five years have shown the efficacy and safety of ZOLADEX. Treatment for greater than five years has not been studied. Both efficacy and tolerability should be considered when deciding on the treatment duration for an individual patient.

Endometrial thinning

Two pivotal trials were conducted with ZOLADEX when used as an endometrial thinning agent prior to endometrial ablation.

In a randomised multicentre trial in 358 women with dysfunctional uterine bleeding, patients were administered either ZOLADEX 3.6 mg implant or sham injection on two occasions. All patients underwent endometrial ablation using loop diathermy alone or in combination with rollerball approximately six weeks after the first injection. The median endometrial thickness prior to surgery was significantly less in the ZOLADEX treated group (1.50 mm) compared to the placebo group (3.55 mm). Six months after surgery, the amenorrhoea rate was statistically significantly higher in the ZOLADEX treated group than the sham group (40% versus 26%). At twelve months follow up, the proportion of patients who remained amenorrhoeic was higher in the ZOLADEX treated group than in the sham group (46% versus 29%) and few gynaecological interventions were required in either group. Although there was no statistically significant difference in improvement in overall menorrhagia (amenorrhoea plus severe hypomenorrhoea) between the ZOLADEX and sham groups, there was a trend in favour of ZOLADEX.

In a randomised trial conducted in 160 women with dysfunctional uterine bleeding, a comparison of one or two implants of ZOLADEX 3.6 mg administered at an interval of four weeks with laser ablation occurring four weeks after ZOLADEX administration was made. The median endometrial thickness prior to surgery was significantly less in the group treated with two implants (0.5 mm) compared to the

group treated with one implant (1 mm). There was no difference in amenorrhoea rates at 24 weeks between groups. Of the patients that completed the trial, 53% and 20% reported hypomenorrhoea and normal menses respectively six months after surgery.

Endometriosis

In a double-blind, multicentre study 345 patients with endometriosis were randomised to one of three treatment groups for a 24 week treatment and 48 week follow-up period. Patients were randomised to receive ZOLADEX alone (HRT0) or with once daily doses of either 0.3 mg oestrogen/5 mg medroxyprogesterone acetate (MPA) (HRT1) or 0.625 mg oestrogen/5 mg MPA (HRT2). Bone mineral density was measured at the lumbar spine (L2-4) using DEXA in most cases, at pre-treatment and at weeks 12, 24, 48 and 72 of the study respectively. The mean percentage losses in bone mineral density at the lumbar spine in the HRT0, HRT1 and HRT2 groups at 12 weeks were 2.1%, 1.1% and 0.8%, at 24 weeks 4.1%, 1.9% and 1.6%, at 48 weeks (eg 24 weeks post treatment follow-up) 2.8%, 1.7% and 1.2% and at 72 weeks (eg 48 weeks post treatment follow-up) 1.7%, 1.2% and 0.5% respectively.

The mean percentage loss in BMD at the lumbar spine was statistically significantly lower in the two HRT treatment groups than in the ZOLADEX alone group ($p<0.001$ at 12 and 24 weeks and $p=0.03$ at week 48 respectively). Decreases in the mean values from baseline occurred in all three treatment groups with no statistically significant differences between the groups during the 24 week treatment period for both the total pelvic symptom scores and the total subjective symptom scores.

At week 12 there was a higher percentage of patients in the ZOLADEX alone group than in either of the HRT groups with hot flushes (94.8%, 56.2% and 45.2% respectively). At week 24 there was a higher percentage of patients with vaginal dryness in the ZOLADEX alone group (51.4%) than in the lower dose HRT group (39.4%) and the higher dose HRT group (25.55%) respectively. The study showed that ZOLADEX plus HRT was as effective as ZOLADEX alone in relieving pelvic symptoms of endometriosis and reduced both the loss of BMD and the physiologic side effects of hot flushes and vaginal dryness.

Assisted reproduction

When ZOLADEX 3.6 mg is used for assisted reproduction, the trials and literature reports consistently show higher success rates than human menopausal gonadotrophin (hMG) alone, or hMG in combination with clomiphene citrate. In this setting, ZOLADEX 3.6 mg is effective in suppression of ovarian activity with pregnancy and live birth rates comparable with other gonadotrophin releasing hormone agonists.

INDICATIONS

Prostate cancer

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

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

Breast cancer

Treatment of advanced breast cancer (T3b, T4 or any T with N2, 3 or M+) in premenopausal women suitable for hormonal manipulation.

Adjuvant therapy in early breast cancer, in pre- and perimenopausal women suitable for hormonal manipulation.

Endometriosis

In the management of visually proven endometriosis to reduce symptoms including pain and the size and number of endometrial lesions.

Uterine fibroids

In the management of fibroids, ZOLADEX shrinks the lesions and reduces the symptoms, including pain. ZOLADEX also increases the haemoglobin concentration and haematocrit in women with anaemia attributable to menorrhagia. It is used as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss.

Endometrial thinning

Use as an endometrial thinning agent prior to endometrial ablation.

Assisted Reproduction

Pituitary down regulation in preparation for controlled ovarian superstimulation.

CONTRAINDICATIONS

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

Pregnancy and lactation (see **Use in Pregnancy and Use in lactation**)

PRECAUTIONS

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

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**).

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

Currently, there are no clinical data on the effects of treating benign gynaecological conditions with ZOLADEX 3.6 mg for periods in excess of six months.

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 signs and symptoms, which can be managed symptomatically. Rarely, patients with bony metastases have developed hypercalcaemia on initiation of therapy.

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.

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.

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.

Endometrial thinning

The use of ZOLADEX may cause an increase in cervical resistance and care should be taken when dilating the cervix. When ZOLADEX is used as a pre-thinning agent prior to endometrial ablation, clinical trials demonstrate an increased incidence of operative complications (such as cervical tears) related to cervical resistance.

Bone mineral density

The use of ZOLADEX causes a loss of bone mineral density. Currently available data suggest that partial recovery of bone loss occurs on cessation of therapy. The following comments are available for:

Endometriosis. In patients receiving ZOLADEX for the treatment of endometriosis, the addition of hormone replacement therapy (a daily oestrogenic agent and a progestogenic agent) has been shown to reduce bone loss in the lumbar spine but not in the femoral neck. Furthermore, hormone replacement therapy has been demonstrated to reduce the vasomotor symptoms in patients receiving ZOLADEX. If HRT is to be used, the Product Information for the particular HRT to be used should be reviewed before starting treatment. Despite the addition of hormone replacement therapy, there are no clinical data on the effects on bone of treating benign gynaecological conditions with ZOLADEX for a continuous period in excess of six months or with repeat courses. Therefore no repeat courses of ZOLADEX (or any other LHRH agonist) should be administered following the initial 6 months course of ZOLADEX therapy without assessment of the risk of developing osteoporosis. Current data suggest that at least 2 years are required between courses of treatment.

Early breast cancer. Following two years treatment for early breast cancer, the average loss of BMD 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 women 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, women 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.

Ovarian hyperstimulation

ZOLADEX should only be administered as part of a regimen for assisted reproduction under the supervision of a specialist experienced in the area. As with other LHRH agonists, there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of ZOLADEX in combination with gonadotrophins. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. Human chorionic gonadotrophin (hCG) should be withheld, if appropriate.

As there are relatively few data in patients with polycystic ovarian syndrome, caution in using ZOLADEX is recommended as these patients are at a greater risk of developing OHSS.

Pregnancy should be excluded before ZOLADEX is used for assisted reproduction. When ZOLADEX is used in this setting (ie for assisted reproduction), there is no clinical evidence to suggest a causal association between ZOLADEX and any subsequent abnormalities of oocyte development or pregnancy and outcome.

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.

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.

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.

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

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 Category D - (see CONTRAINDICATIONS)

ZOLADEX should not be used in pregnancy as there is a theoretical risk of abortion or fetal abnormality if LHRH agonists are used during pregnancy. Potentially fertile women should be examined carefully before treatment to exclude pregnancy. A pregnancy test should be performed prior to administering the ZOLADEX implant. Non-hormonal methods of contraception should be employed during therapy and it is generally recommended that the initial injection should be given early in the follicular phase of the menstrual cycle except in the case of assisted reproduction when the initial injection may be given in the luteal or follicular phase of the menstrual cycle, in accordance with the specialist's normal practice.

Subcutaneous injection of goserelin into pregnant rats or rabbits at doses greater than 10 to 20 µg/kg/day has been shown to cause foetal deaths and termination of pregnancy. Parturition in rats is inhibited at doses greater than 0.01 µg/kg/day. There was no conclusive evidence of any teratogenic effects in animals, although a low incidence of head malformations in rabbits may have been secondary to the endocrine effects of the drug.

Use in Lactation - (see CONTRAINDICATIONS)

The use of goserelin during breast feeding is not recommended.

A study in lactating rats showed that drug-related material is excreted in milk after subcutaneous administration of radiolabelled goserelin acetate; most of the excreted radioactivity was associated with inactive metabolites, although small amounts of parent drug were detectable. There are no adequate studies on the effects of goserelin administered to lactating women.

Interactions with other drugs

None known.

Effects on laboratory tests

None known.

Effect on ability to drive and use machinery

There is no evidence that ZOLADEX 3.6 mg results in impairment of ability to drive or operate machinery.

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)	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] Blood pressure abnormal[b]
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a]	Hyperhidrosis[a], acne[i]
	Reproductive system and breast disorders	Erectile dysfunction N/A N/A Breast tenderness Gynaecomastia	N/A Vulvovaginal dryness Breast enlargement N/A N/A
	General disorders and administration site conditions	(see Common)	Injection site reactions
	Psychiatric disorders	N/A N/A	Mood altered Depression

Frequency	System Order Class	Event (Males)	Event (Females)
	Nervous system disorders	Paraesthesia N/A	Paraesthesia Headache
	Investigations	Bone density decreased	Bone density decreased
Common (≥ 1% and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired[c]	NA
	Nervous system disorders	Spinal cord compression	N/A
	Psychiatric disorders	Mood swings	N/A
	Renal and urinary tract disorders	Incontinence and urinary frequency (after radiotherapy)	N/A
	Skin and subcutaneous tissue disorders	Rash[d] (see Unknown)	Rash[d] Alopecia[g]
	Musculoskeletal, connective tissue and bone disorders	Bone pain[e] Arthralgia	N/A Arthralgia
	Cardiac disorders	Cardiac failure[f] Myocardial infarction[f]	N/A N/A
	General disorders and administration site conditions	N/A Injection site reaction	Tumour flare, tumour pain (see Very common)
	Investigations	Weight increased	Weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity	Drug hypersensitivity
	Renal and urinary tract disorders	Ureteric obstruction	N/A
	Metabolism and nutrition disorders	N/A	Hypercalcaemia
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N/A	Degeneration of uterine fibroid

Frequency	System Order Class	Event (Males)	Event (Females)
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction	Anaphylactic reaction
	Reproductive system and breast disorders	N/A N/A	Ovarian cyst Ovarian hyperstimulation syndrome
	Endocrine disorders	Pituitary haemorrhage/infarction	Pituitary haemorrhage/infarction
Very rare (<0.01%)	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pituitary tumour	Pituitary tumour
	Psychiatric disorders	Psychotic disorders	Psychotic disorders
Unknown	Skin and subcutaneous tissue disorders	Alopecia[h]	(see Common)

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 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.

h Particularly loss of body hair, an expected effect of lowered androgen levels.

i In most cases acne was reported within one month after the start of ZOLADEX.

DOSAGE AND ADMINISTRATION

Caution should be taken while inserting ZOLADEX into the interior 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**).

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.

Prostate cancer

One 3.6 mg implant of ZOLADEX injected subcutaneously into the anterior abdominal wall, every 28 days.

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

Breast cancer

Early breast cancer

ZOLADEX 3.6 mg therapy as an alternative to combination chemotherapy.

One 3.6 mg implant of ZOLADEX injected subcutaneously into the anterior abdominal wall, every 28 days, for 2 years.

Adjuvant ZOLADEX 3.6 mg therapy post combination chemotherapy.

One 3.6 mg implant of ZOLADEX injected subcutaneously into the anterior abdominal wall, every 28 days, for 5 years.

Advanced breast cancer

One 3.6 mg implant of ZOLADEX injected subcutaneously into the anterior abdominal wall, every 28 days.

Endometrial thinning

When used as an endometrial thinning agent prior to endometrial ablation, ZOLADEX 3.6 mg should be administered as one implant followed by surgery at four weeks or a course of two implants inserted four weeks apart followed by

surgery within two to four weeks of the insertion of the second implant. A second implant may be required to allow flexible surgical timing.

Benign gynaecological disorders

The recommended duration of therapy is six months. As safety data are not available for subsequent courses or courses longer than six months re-treatment cannot be recommended at this point in time. If longer duration of treatment is contemplated, an assessment of the risk of significant changes in bone mass should be made for each patient and the measurement of bone density considered (see **PRECAUTIONS**). The risks and benefits of treatment with ZOLADEX should be considered for each patient and discussed between patient and prescriber.

In the treatment of uterine fibroids, ZOLADEX may be used for a period of 3 to 6 months. Because it is used as an adjunct to surgery, no data are available on the safety or efficacy of subsequent courses of treatment.

Assisted reproduction

Once pituitary down regulation has been achieved with ZOLADEX (long protocol) controlled ovarian superstimulation and oocyte retrieval should be carried out. The protocol employed throughout should follow normal practice.

Elderly

No dosage adjustment is necessary in the elderly

Children

Not indicated for use in children.

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment.

OVERDOSAGE

There is limited experience of overdosage in humans. In cases where ZOLADEX has unintentionally been re-administered 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

ZOLADEX 3.6 mg SafeSystem™ Implant is supplied as a sterile, biodegradable cylindrical implant containing the equivalent of 3.6 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.

Storage

Store below 25°C.

POISON SCHEDULE OF THE DRUG

S4

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
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Alma Road
NORTH RYDE NSW 2113

DATE OF APPROVAL

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