NEW ZEALAND DATA SHEET

NAME OF MEDICINE

ZOLADEX 10.8 mg
Goserelin (present as goserelin acetate) 10.8 mg injection.

PRESENTATION

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

USES

ACTIONS

ZOLADEX (D-Ser(But)^{6}Azgly^{10} LHRH) is a synthetic analogue of naturally occurring luteinising-hormone releasing hormone (LHRH). On chronic administration, ZOLADEX 10.8 mg results in inhibition of pituitary luteinising-hormone secretion leading to a fall in serum testosterone concentrations in men and serum oestradiol concentrations in women. Initially ZOLADEX 10.8 mg, like other LHRH agonists, may transiently increase serum testosterone concentrations in men and serum oestradiol concentrations in women.

In men by around 21 days after the first depot injection, testosterone concentrations have fallen 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 depot injection and remain suppressed until the end of the treatment period. In patients with oestradiol already suppressed by an LHRH analogue, suppression is maintained on the change of therapy to ZOLADEX 10.8 mg. Suppression of oestradiol is associated with a response in endometriosis and uterine fibroids and will result in amenorrhoea in the majority of patients.

During early treatment with ZOLADEX some women may experience vaginal bleeding of variable duration and intensity. Such bleeding probably represents oestrogen withdrawal bleeding and is expected to stop spontaneously.

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

Effect in prostate cancer – Adjuvant and neoadjuvant ZOLADEX therapy in combination with radiotherapy

Four 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 two independent collaborative oncology groups (European Organisation for Research and Treatment of Cancer [EORTC] and the Radiation Therapy Oncology Group [RTOG]), 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 neoadjuvant 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)*
Treatment	Zoladex* + RT	Zoladex*# + RT	Zoladex *§ + RT	Zoladex*§ (neo) + RT + Zoladex* alone (adjuvant)
Comparator	RT alone + Zoladex at relapse	RT alone	RT alone	Zoladex*§ (neo) only + RT
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 2 months prior to & during RT
Patient population	T1-2N+ & T3 (any N); Lesions <25cm^3; prior prostatectomy allowed^	T1-2N0-X (G3) & T3-4N0 (any G)	T2b-4M0; N+ allowed†; Lesions ≥25cm^3	T2c-T4; PSA <150ng/mL; N+ allowed†; KS ≥70
Median follow-up	7.6 years[a]	5.5 years[b]	6.7 years[c]	5.8 years[d]

*T, N – Tumour, node in accordance with the UICC classification; G – WHO grade; *3.6 mg sc every 4 weeks; # plus 1 month of oral cyproterone acetate 150mg/day initiated 1 week prior to Zoladex to prevent flare; RT – radiotherapy; § combined with oral flutamide (250mg 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, In J Radiation Oncol Biol Phys 54: 1302-1310; [d]Hanks et al 2003, JCO 21: 3972-3978

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 therapy (2 years) also significantly improved disease-free survival but not overall survival compared to radiotherapy alone (Table 5).

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*
	Zoladex +RT	*RT alone*	*[95% CI]*
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

PHARMACOKINETICS

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

INDICATIONS

ZOLADEX 10.8 mg is indicated for the management of:

1. Prostate cancer suitable for hormonal manipulation.

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

3. Endometriosis: ZOLADEX alleviates symptoms including pain, and reduces the size and number of endometrial lesions.

4. Uterine fibroids: ZOLADEX shrinks the lesions, reduces symptoms including pain, and causes cessation of menses in the majority of patients thereby improving haematological status when previous heavy menstrual loss has caused anaemia.

DOSAGE AND ADMINISTRATION

For correct administration of ZOLADEX, see instructions on the administration card (also see INSTRUCTIONS FOR USE/HANDLING).

ADULT MEN

One depot of ZOLADEX 10.8 mg injected subcutaneously into the anterior abdominal wall every 3 months.

Adjuvant and/or neoadjuvant Zoladex therapy in combination with radiotherapy may include short-term use of an anti-androgen to prevent flare (see ACTIONS).

ADULT WOMEN

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

CHILDREN

ZOLADEX 10.8 mg is not indicated for use in children.

ELDERLY

No dosage adjustment is necessary in the elderly.

RENAL AND HEPATIC IMPAIRMENT

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

CONTRAINDICATIONS

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

Pregnancy and lactation (See PREGNANCY AND LACTATION).

WARNINGS AND PRECAUTIONS

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

The use of ZOLADEX 10.8 mg in men at particular risk of developing ureteric obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. If spinal cord compression or renal impairment due to ureteric obstruction are present or develop, specific standard treatment of these complications should be instituted.

Initially ZOLADEX 10.8 mg, like other LHRH agonists, transiently increases serum testosterone. Some patients may experience a temporary increase in bone pain, which can be managed symptomatically.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus. Consideration should therefore be given to monitoring blood glucose.

An increased risk of developing myocardial infarction and, sudden cardiac death has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease.

The use of LHRH agonists may cause a reduction in bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority. In patients receiving ZOLADEX 3.6 mg 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 mineral loss and vasomotor symptoms. There is no experience of the use of hormone replacement therapy in women receiving ZOLADEX 10.8 mg. In men, preliminary data suggest the use of a bisphosphonate in combination with a LHRH agonist may reduce bone mineral loss.

In women, ZOLADEX 10.8 mg is only indicated for use in endometriosis and fibroids. For female patients requiring treatment with goserelin for other conditions, refer to the prescribing information for ZOLADEX 3.6 mg.

Time to return of menses after cessation of therapy with ZOLADEX 10.8 mg may be prolonged in some patients.

The use of ZOLADEX may cause an increase in cervical resistance and care should be taken when dilating the cervix.

There are no clinical data on the effects of treating benign gynaecological conditions with ZOLADEX for periods in excess of six months.

PREGNANCY

ZOLADEX 10.8 mg should not be used in pregnancy as there is a theoretical risk of abortion or foetal abnormality if LHRH agonists are used during pregnancy. Potentially fertile women should be examined carefully before treatment to exclude pregnancy. Non hormonal methods of contraception should be employed during therapy until menses is resumed. (See WARNINGS AND PRECAUTIONS - time to return of menses).

LACTATION

The use of ZOLADEX 10.8 mg during breast feeding is not recommended.

EFFECT ON ABILITY TO DRIVE AND USE MACHINERY

There is no evidence that ZOLADEX 10.8 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.

Table 6 ZOLADEX 10.8 mg adverse drug reactions by frequency and System Organ Class (SOC)

Frequency Descriptor	SOC	Males	Females
Very Common ~~(≥10%)~~	Psychiatric disorders	Libido decreased[a]	Libido decreased[a]
	Vascular disorders	Hot flush[a]	Hot flush[a]
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a]	Hyperhidrosis[a]
	Reproductive system and breast disorders	Erectile dysfunction	N/A
		N/A	Vulvovaginal dryness
		N/A	Breast enlargement
	General disorders and administration site conditions	(see Common)	Injection site reactions
Common (≥1% and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired[b]	N/A
	Psychiatric disorders	N/A	Mood altered, depression
	Nervous system disorders	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
	Cardiac disorders	Cardiac failure[f] Myocardial infarction[f]	N/A

Frequency Descriptor	SOC	Males	Females
	Vascular disorders	Blood pressure abnormal[c]	Blood pressure abnormal[c]
	Skin and subcutaneous tissue disorders	Rash[d]	Rash[d], alopecia[g]
	Musculoskeletal, connective tissue and bone disorders	Bone pain[e]	N/A
		(see Uncommon)	Arthralgia
	Reproductive system and breast disorders	Gynaecomastia	N/A
	General disorders and administration site conditions	N/A	Tumour flare, tumour pain
		Injection site reaction	(see Very common)
	Investigations	Density decreased, weight increased	Bone density decreased, weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity	Drug hypersensitivity
	Musculoskeletal, connective tissue and bone disorders	Arthralgia	(see Common)
	Renal and urinary disorders	Ureteric obstruction	N/A
	Reproductive system and breast disorders	Breast tenderness	N/A
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction	Anaphylactic reaction
	Reproductive system and breast disorders	N/A	Ovarian cyst
Very rare (<0.01%)	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pituitary tumour	Pituitary tumour
	Endocrine disorders	Pituitary haemorrhage	Pituitary haemorrhage
	Psychiatric disorders	Psychotic disorder	Psychotic disorder
Unknown	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N/A	Degeneration of uterine fibroid
	Skin and subcutaneous tissue disorders	Alopecia[h]	(see Common)

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

[b] A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus.

[c] These may manifest as hypotension or hypertension, have been occasionally observed in patients administered ZOLADEX. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with ZOLADEX. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from ZOLADEX.

[d] These are generally mild, often regressing without discontinuation of therapy.

[e] Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.

[f] Observed in a pharmaco-epidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.

[g] 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.

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

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

INTERACTIONS

None known

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 10.8 mg. If overdosage occurs, this should be managed symptomatically.

PHARMACEUTICAL PRECAUTIONS

STORAGE CONDITIONS

Store below 25°C.

SHELF LIFE

3 years

INSTRUCTIONS FOR USE / HANDLING

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

Before injection, it should be ensured that the implant is visible in the window of the applicator. The plunger should not be withdrawn once the needle is in position. The plunger should be fully depressed to expel the implant into the subcutaneous tissue well away from point of entry and to activate the protective needle sleeve.

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

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

There is one depot per pack.

FURTHER INFORMATION

Following long-term repeated dosing with ZOLADEX, an increased incidence of benign pituitary tumours has been observed in male rats. While this finding is similar to that previously noted in this species following surgical castration, any relevance to humans has not been established.

In mice, long term repeated dosing with multiples of the human dose produced histological changes in some regions of the digestive system manifested by pancreatic islet cell hyperplasia and a benign proliferative condition in the pyloric region of the stomach, also reported as a spontaneous lesion in this species. The clinical relevance of these findings is unknown.

ZOLADEX is a synthetically derived peptide.

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