FINAL PACKAGE INSERT

SCHEDULING STATUS: **S4**

PROPRIETARY NAME (and dosage form):

Zoladex® 3,6 mg (Injection)

COMPOSITION:

Each ZOLADEX 3,6 mg contains goserelin acetate equivalent to 3,6 mg goserelin base.

PHARMACOLOGICAL CLASSIFICATION:

A 21.10 Trophic hormones

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Goserelin is a synthetic analogue of naturally occurring luteinizing hormone releasing hormone (LHRH), a decapeptide found in the hypothalamus. LHRH controls the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. On chronic administration goserelin results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum oestradiol concentrations in females. Initially, goserelin transiently increases 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 continuous treatment every 28 days.

In women serum oestradiol concentrations are suppressed by around 21 days after the first depot

injection and, with continuous treatment every 28 days, remain suppressed at levels comparable to those observed in postmenopausal women. This suppression is associated with endometrial thinning and suppression of follicular development within the ovary. It will result in amenorrhoea in the majority of patients.

Pharmacokinetic properties:

The bioavailability of goserelin is almost complete. Administration of a depot every 4 weeks ensures that effective concentrations are maintained with no accumulation. Goserelin 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 renal failure. For the compound given monthly in a depot formulation, this change will have minimal effect. Hence, no change in dosing is necessary in these patients. There is no significant change in pharmacokinetics in patients with hepatic failure.

INDICATIONS:

Prostate cancer suitable for hormonal manipulation.

Advanced or metastatic breast cancer suitable for hormonal manipulation, in pre- and perimenopausal women.

Early breast cancer: ZOLADEX 3,6 mg is indicated as adjuvant therapy to surgery and/or radiotherapy in pre-menopausal women with oestrogen receptor positive early breast cancer suitable for hormonal manipulation, as an alternative to chemotherapy.

Relief of clinical symptoms associated with endometriosis.

Reduction of uterine fibroid size before surgery.

Endometrial Thinning:

ZOLADEX is indicated for the pre-thinning of the uterine endometrium prior to endometrial ablation for severe dysfunctional uterine bleeding, which cannot be managed by non-surgical intervention and if unsuitable for immediate surgical intervention.

Assisted reproduction:

Pituitary downregulation in preparation for superovulation.

CONTRA-INDICATIONS:

Known severe hypersensitivity to the active substance or to any of the excipients of this product (see "Pregnancy and lactation").

Children:

ZOLADEX is not indicated for use in children, as safety and efficacy have not been established.

WARNINGS:

Patients with proven non-hormone dependent cancer e.g. those who have failed to respond to previous surgical castration or oestrogens, are less likely to respond to ZOLADEX than previously untreated patients.

ZOLADEX may cause an increase in uterine cervical resistance, which may result in difficulty when the cervix is dilated. Care should be taken when dilating the cervix.

The safety and efficacy of ZOLADEX for gynaecological conditions have not been established for periods exceeding 6 months.

The use of LHRH agonists is associated with a loss of bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority. Preliminary data suggest the use of ZOLADEX in combination with tamoxifen in patients with breast cancer may reduce bone mineral loss. In women 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 mineral density loss and vasomotor symptoms.

In men, preliminary data suggest the use of a biphosphonate in combination with an LHRH agonist may reduce bone mineral loss.

Assisted reproduction:

Pregnancy should be excluded before ZOLADEX 3,6 mg is used for assisted reproduction. The clinical data from use of ZOLADEX 3,6 mg are limited, but the available evidence suggests there is no causal association between ZOLADEX and any subsequent abnormalities of oocyte development or pregnancy and outcome.

ZOLADEX 3,6 mg should only be administered as part of a regimen for assisted reproduction under the supervision of a specialist in the area.

There have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of ZOLADEX 3,6 mg, 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.

It is recommended that ZOLADEX 3,6 mg should be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome as follicle recruitment may be increased in these patients.

PREGNANCY AND LACTATION:

Pregnancy:

ZOLADEX 3,6 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.

Lactation:

The use of ZOLADEX 3,6 mg during breast feeding is not recommended.

DOSAGE AND DIRECTIONS FOR USE:

Adults, including the elderly:

One 3,6 mg depot of ZOLADEX injected subcutaneously into the anterior abdominal wall, every 28 days.

Note:

1. Gynaecological conditions should be treated for a period of at most 6 months only, since at present there are no clinical data for longer treatment periods. The use of ZOLADEX may cause a loss of bone mineral density.
2. *Endometrial Thinning:* 1 or 2 ZOLADEX 3,6 mg doses administered 4 weeks apart. When 1 depot is administered, surgery should be performed at 4 weeks. The second depot may be required for the patient with a large uterus or to allow flexible timing of surgery. When 2 depots are administered, surgery should be performed within 2 weeks after the administration of the second depot.

Assisted reproduction: Once pituitary down regulation has been achieved with ZOLADEX 3,6 mg, superovulation and oocyte retrieval should be carried out in accordance with normal practice.

No dosage adjustment is necessary for patients with renal impairment, hepatic impairment, nor for the elderly.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Frequency Classification	**System Organ Class**	**Adverse Reaction**	
		Female	**Male**
Very common > 10%	Nervous system disorders	[1]Headaches[2]	Non-specific paraesthesias
	Psychiatric disorders	Depression[4], [1]loss of libido[2]	[3]Decrease in potency, sexual dysfunction
	Reproductive system and breast disorders	[1]Breast size change, vaginal dryness[2]	
	Skin and subcutaneous tissue disorders	[1]Sweating[2]	[3]Sweating
Very common > 10% (continued)	Vascular disorders	[1]Hot flushes[2], transient increases in systolic and diastolic blood pressure levels[5]	[3]Hot flushes

Frequency Classification	**System Organ Class**	**Adverse Reaction**	
		Female	**Male**
Common 1-10%	Muscoskeletal and connective tissue disorders		Loss of bone mineral density[5], increase in bone pain[6]
	Reproductive system and breast disorders		[3]Breast swelling
	Neoplasms benign, malignant and unspecified	Increase in signs and symptoms in breast cancer	
	Skin and subcutaneous tissue disorders		Skin rashes[7]
Uncommon 0,1-1%	Metabolism and nutrition disorders	Hypercalcaemia on initiation of therapy[8]	
	Muscoskeletal and connective tissue disorders		Arthralgia
	Nervous system disorder		Spinal cord compression
	Renal and urinary disorders		Ureteric obstruction
	Reproductive system and breast disorders		Breast tenderness

Frequency Classification	**System Organ Class**	**Adverse Reaction**	
		Female	**Male**
Rare < 0,1%	Endocrine disorders		Pituitary apoplexy[9]
	Immune system disorders	Hypersensitivity reactions[10]	Hypersensitivity reactions[10]
	Reproductive system and breast disorders	Ovarian hyperstimulation syndrome[11]	

1. Following the reduction of serum oestradiol consequent to ZOLADEX administration, these adverse effects are frequent.
2. These side-effects may decrease in intensity and in incidence with prolonged therapy.
3. Reduction of serum testosterone may result in these side effects.
4. Following the reduction of serum oestradiol consequent to ZOLADEX administration, these adverse effects are frequent. Mood changes, including depression.
5. Changes in blood pressure, manifested 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. In hypertensive patients, blood pressure should be monitored more frequently and therapy may have to be adjusted.
6. The use of ZOLADEX may cause loss of bone mineral density. Initially, some patients may experience a temporary increase in bone pain, which can be managed symptomatically.

7. Skin rashes have been generally mild and often regressed without discontinuation of therapy, ichthyosis.
8. Rarely breast cancer patients with bony metastases have developed hypercalcaemia on initiation of therapy.
9. Less frequently cases of pituitary apoplexy have been reported following initial administration.
10. Hypersensitivity reactions, which may include anaphylaxis, angioedema, urticaria, eczema, bronchospasm and maculopapular rash.
11. There have been reports of ovarian cyst formation and, when ZOLADEX 3,6 mg is used in combination with gonadotrophins, of ovarian hyperstimulation syndrome (OHSS).

Blood lipids (total cholesterol, low density cholesterol, triglycerides) may increase.

Occasional local reactions including mild bruising at the subcutaneous injection site, have been reported.

The following occasional serious adverse effects have been associated with the use of ZOLADEX: Interstitial lung infiltrates, joint swelling and effusions in joints, carpal tunnel syndrome, and erythema multiforme.

Females:

Decrease in bone density (see “Warnings”).

Pelvic pain, sometimes severe and related to haemorrhage into uterine fibromyoma may occur. Dyspareunia, dysmenorrhoea as well as menorrhagia, uterine and vaginal bleeding have been observed in patients treated for uterine fibroids.

Initially, some patients may experience a temporary increase in signs and symptoms, which can be managed symptomatically.

During ZOLADEX treatment, some women may experience vaginal bleeding of variable duration and intensity. Such bleeding usually represents oestrogen withdrawal bleeding and is expected to stop spontaneously, usually after the first 2 doses, but may also be caused by degenerating fibromyoma. Spotting is common.

In women with fibroids, degeneration of fibroids may occur resulting in abdomino-pelvic pain, low grade fever, continual bleeding and occasional enlargement of the fibroid and ascites.

During treatment with LHRH analogues patients will enter the menopause. Menses may not return on cessation of therapy. The median time for return of menses after treatment with ZOLADEX is 70 days from time of last injection.

Following the reduction of serum oestradiol consequent to ZOLADEX administration, the following adverse effects are frequent:
Insomnia, tiredness
Weight gain

These side-effects may decrease in intensity and in incidence with prolonged therapy.

In clinical trials where patients were questioned about specific adverse events (endometriosis 2 studies; fibromyomata 1 study), acne, seborrhoea, oily hair, hirsutism and oedema were also reported frequently.

Migraine attacks may be precipitated occasionally. Confusional states have been reported.

Special precautions:

Following long-term repeated dosing with ZOLADEX, an increased incidence of benign pituitary tumours has been observed in male rats. Whilst this finding is similar to that previously noted in this species following surgical castration, any relevance to man 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. This is 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.

Males:

The use of ZOLADEX in patients 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.

Effects on ability to drive and use machines:

There is no evidence that ZOLADEX results in impairment of these activities.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

White to cream coloured cylindrical pieces of rigid polymeric material, supplied in a pre-loaded single-dose disposable syringe applicator.

PRESENTATION:

The depot is supplied in a pre-loaded single-dose disposable syringe applicator.

STORAGE INSTRUCTIONS:

Store in the sealed package at a temperature at or below 25 °C. Keep out of reach of children.

REGISTRATION NUMBER:

U/21.10/163

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTATION:

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

7 April 2006

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Ref: Zoladex 3,6 mg – EPI (22-02-2006)

CDS: 12 Feb 2003

Inclusion of Namibia + Botswana registration details (01-11-2010)

NAMIBIA: NS2 Reg. No.: 90/21.10/00294

BOTSWANA: S2 Reg. No.: B9304875