Goserelin

Zoladex® 3.6 mg

3.6 mg Depot in Pre-filled Syringe

For Subcutaneous Injection

LHRH Agonist

1. NAME OF THE MEDICINAL PRODUCT

Goserelin (ZOLADEX®), depot, 3.6 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Goserelin acetate (equivalent to 3.6 mg goserelin)

3. PHARMACEUTICAL FORM

Depot, pre-filled syringe

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prostate cancer: Goserelin (ZOLADEX) 3.6 mg is indicated in the management of prostate cancer suitable for hormonal manipulation.

Breast cancer: Goserelin (ZOLADEX) 3.6 mg is indicated in the management of breast cancer in pre and perimenopausal women suitable for hormonal manipulation.

Endometriosis: In the management of endometriosis, Goserelin (ZOLADEX) 3.6 mg alleviates symptoms, including pain, and reduces the size and number of endometrial lesions.

Uterine fibroids: In the management of fibroids, Goserelin (ZOLADEX) 3.6 mg shrinks the lesions, improves the patient's haematological status and reduces symptoms, including pain. 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. As a pre-thinning agent Goserelin (ZOLADEX) 3.6 mg should be administered as two depots,

four weeks apart, with surgery planned for between zero and two weeks after the second depot injection.

Assisted reproduction: Pituitary downregulation in preparation for superovulation.

4.2 Dosage and method of administration

Caution should be taken while inserting Goserelin (ZOLADEX) into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

Use extra care when administering Goserelin (ZOLADEX) to patients with a low BMI and/or who are receiving full anticoagulation medication (see section 4.4 Special warnings and special precautions for use).

For correct administration of Goserelin (ZOLADEX), see instructions on the instruction card (see section 6.6 Instructions for use, handling and disposal).

Adults: One 3.6 mg depot of Goserelin (ZOLADEX) injected subcutaneously into the anterior abdominal wall, every 28 days.

Assisted reproduction: Once pituitary downregulation has been achieved with Goserelin (ZOLADEX) 3.6 mg, superovulation and oocyte retrieval should be carried out in accordance with normal practice.

Elderly: No dosage adjustment is necessary in the elderly.

Renal Impairment: No dosage adjustment is necessary for patients with renal impairment.

Hepatic Impairment: No dosage adjustment is necessary for patients with hepatic impairment.

Children: Not indicated for use in children.

4.3 Contraindications

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

See section 4.6 Pregnancy and lactation.

4.4 Special warnings and special precautions for use

Goserelin (ZOLADEX) 3.6 mg 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 Goserelin (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 Goserelin (ZOLADEX) to patients with a low BMI and/or receiving full anticoagulation medication (see section 4.2 Dosage and method of administration).

The use of Goserelin (ZOLADEX) 3.6 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.

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. Preliminary data suggest the use of Goserelin (ZOLADEX) in combination with tamoxifen in patients with breast cancer may reduce bone mineral loss. In patients receiving Goserelin (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 bisphosphonate in combination with an LHRH agonist may reduce bone mineral loss.

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.

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

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

Androgen deprivation therapy may prolong the QT interval, although a causal association has not been established with Goserelin (ZOLADEX). In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may prolong the QT interval (see section 4.5 Interaction with other medicinal products and other forms of interaction) physicians should assess the benefit risk ratio including the potential for Torsade de Pointes prior to initiating Goserelin (ZOLADEX).

Assisted Reproduction: Goserelin (ZOLADEX) 3.6 mg 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 Goserelin (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 Goserelin (ZOLADEX) 3.6 mg be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome as follicle recruitment may be increased.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Goserelin (ZOLADEX) with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de Pointes should be carefully evaluated (see section 4.4 Special warnings and special precautions for use).

4.6 Pregnancy and lactation

Pregnancy: Goserelin (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 until menses resume.

Pregnancy should be excluded before Goserelin (ZOLADEX) 3.6 mg is used for assisted reproduction. When Goserelin (ZOLADEX) 3.6 mg is used in this setting, there is no clinical evidence to suggest a causal association between Goserelin (ZOLADEX) and any subsequent abnormalities of oocyte development or pregnancy and outcome.

Lactation: The use of Goserelin (ZOLADEX) 3.6 mg during breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Table 1 Goserelin (ZOLADEX) 3.6 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] , acne [i]
	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]	NA

Frequency Descriptor	SOC	Males	Females
	Psychiatric disorders	Mood swings	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
	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	Bone density decreased, weight increased	Bone density decreased, weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity	Drug hypersensitivity
Uncommon (continued)	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
	Metabolism and nutrition disorders	N/A	Hypercalcaemia
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction	Anaphylactic reaction
	Reproductive system and breast disorders	N/A	Ovarian cyst
		N/A	Ovarian hyperstimulation syndrome

Frequency Descriptor	SOC	Males	Females
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 with Goserelin (ZOLADEX). The changes are usually transient, resolving either during continued therapy or after cessation of therapy with Goserelin (ZOLADEX). Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from Goserelin (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.

[i] In most cases acne was reported within one month after the start of Goserelin (ZOLADEX).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Goserelin (ZOLADEX) (D-Ser(But)^{6} Azgly^{10} LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration Goserelin (ZOLADEX) 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 (ZOLADEX) like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum oestradiol concentration in women.

During early treatment with Goserelin (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.

In men by around 21 days after the first depot 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 depot 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 LHRH analogues patients may enter the natural menopause. Rarely some women do not resume menses on cessation of therapy.

5.2 Pharmacokinetic properties

The bioavailability of Goserelin (ZOLADEX) is almost complete. Administration of a depot every four weeks ensures that effective concentrations are maintained with no tissue accumulation. Goserelin (ZOLADEX) is poorly protein bound and has a serum elimination half-life of two to four hours in subjects with normal renal function. The half-life is increased in patients with impaired renal function. 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.

5.3 Preclinical safety data

Following long-term repeated dosing with Goserelin (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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MF2439

Lactide/glycolide co-polymer

6.2 Incompatibilities

None known.

6.3 Shelf-life

Please refer to the outer carton.

6.4 Special precautions for storage

Store at temperatures below 25ºC.

6.5 Nature and contents of container

Single dose syringe applicator assembled with a protective sleeve in a sealed pouch which contains a desiccant.

6.6 Instructions for use, handling and disposal

For correct administration of Goserelin (ZOLADEX), see instructions on the instruction card.

Use as directed by the prescriber. Use extra care when administering Goserelin (ZOLADEX) to patients with a low BMI and/or who are receiving full anticoagulation medication (see section 4.4 Special warnings and special precautions for use).

Use only if pouch is undamaged. Use immediately after opening the pouch.

Instructions for inclusion on the instruction card as applicable:

The following information is intended for medical or healthcare professionals only:

Goserelin (ZOLADEX) is administered by subcutaneous injection - read and understand all the instructions fully prior to administration.

1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare the injection site according to the local policy and procedure.

NOTE: Caution should be taken while injecting Goserelin (ZOLADEX) into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches; very thin patients may be at higher risk of vascular injury.

2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light.
   Check that at least part of the Goserelin (ZOLADEX) implant is visible. **(Figure 1).**

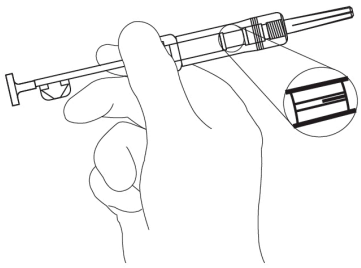

Figure 1.

3. Grasp the plastic safety tab and pull away from the syringe, and discard. **(Figure 2).** Remove the needle cover. **Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the Goserelin (ZOLADEX) implant.**

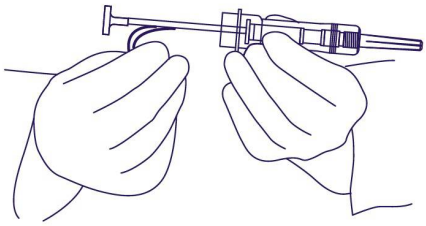

Figure 2.

4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the patient's skin and insert the needle at a slight angle (30 to 45 degrees) to the skin. With the opening of the needle facing up, **insert needle into the subcutaneous tissue** of the anterior abdominal wall below the navel line, until the protective sleeve touches the patient's skin. **(Figure 3).**

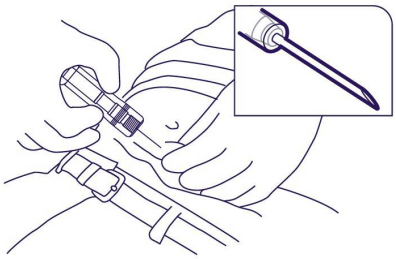

Figure 3.

NOTE: The Goserelin (ZOLADEX) syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and immediately control any resultant bleeding, monitoring the patient for signs or symptoms of abdominal haemorrhage. After ensuring the patient is haemodynamically stable another Goserelin (ZOLADEX) implant may be injected with a new syringe elsewhere. Use extra care when administering Goserelin (ZOLADEX) to patients with a low BMI and/or to patients receiving full dose anticoagulation.

5. **Do not penetrate into muscle or peritoneum.** Incorrect grip and angle of presentation is shown **(Figure 4.)**

Figure 4.

6. Depress the plunger **fully**, until you can depress no more, to discharge the Goserelin (ZOLADEX) implant and to activate the protective sleeve. You may hear a 'click' and will feel the protective sleeve automatically begin to slide to cover the needle. If the plunger is not depressed fully, the protective sleeve will **NOT** activate.

   NOTE: The needle does not retract.

7. Holding the syringe as shown in **Figure 5,** withdraw the needle and allow protective sleeve to continue to slide and cover needle.
   Dispose of the syringe in an approved sharps collector.

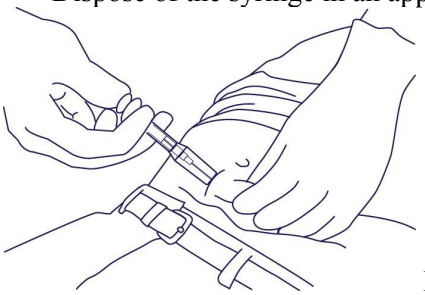

Figure 5.

NOTE: In the unlikely event of the need to surgically remove a Goserelin (ZOLADEX) implant, it may be localized by ultrasound.

6.7 Availability

Goserelin (ZOLADEX) 3.6 mg Depot in Pre-filled Syringe for SC Inj. – Box of 1's.

7. REGISTRATION NUMBER

DR-XY16736

8. DATE OF FIRST AUTHORIZATION

2 August 1999

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The

patient should seek medical attention immediately at the first sign of any adverse drug reaction.

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Imported by the Marketing Authorization Holder
AstraZeneca Pharmaceuticals (Phils.), Inc.
16th Floor, Inoza Tower, 40th Street,
Bonifacio Global City, Taguig, Philippines
Manufactured by AstraZeneca UK Ltd., Macclesfield, Cheshire, UK