Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zoladex 3.6 mg Implant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Goserelin acetate equivalent to 3.6 mg goserelin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant

White to cream-coloured cylindrical implant in a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

(i) Prostate Cancer: Zoladex 3.6mg is indicated in the management of prostate cancer suitable for hormonal manipulation.

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

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

(iv) Uterine fibroids: In the management of fibroids, Zoladex 3.6mg 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.

(v) Endometrial Thinning: Use as an endometrial thinning agent prior to endometrial ablation. As a prethinning agent Zoladex 3.6mg should be administered as two depots, four weeks apart, with surgery planned for between zero and two weeks after the second depot injection.

(vi) Assisted Reproduction: Pituitary downregulation in preparation for superovulation.

4.2 Posology and method of administration

Posology

Adults:	One 3.6 mg depot of Zoladex injected subcutaneously into the anterior abdominal wall every 28 days
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
Assisted Reproduction:	Once pituitary downregulation has been achieved with Zoladex 3.6 mg, superovulation and oocyte retrieval should be carried out in accordance with normal practice
Paediatric population:	Not indicated for use in children

Endometriosis:
Endometriosis should be treated for a period of six months only, since at present there are no clinical data for longer treatment periods. Repeat courses should not be given due to concern about loss of bone mineral density. 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 mineral density loss and vasomotor symptoms.

Endometrial thinning:
For use in endometrial thinning: four or eight weeks treatment. The second depot may be required for the patient with a large uterus or to allow flexible surgical timing.

Uterine fibroids:
For women who are anaemic as a result of uterine fibroids: Zoladex 3.6 mg depot with supplementary iron may be administered for up to three months before surgery.

Assisted reproduction:
Zoladex 3.6 mg is administered to downregulate the pituitary gland, as defined by serum estradiol levels similar to those observed in the early follicular phase (approximately 150 pmol/l). This will usually take between 7 and 21 days.
When downregulation is achieved, superovulation (controlled ovarian stimulation) with gonadotrophin is commenced. The downregulation achieved with a depot agonist is more consistent suggesting that, in some cases, there may be an increased requirement for gonadotrophin. At the appropriate stage of follicular development, gonadotrophin is stopped and human chorionic gonadotrophin (hCG) is administered to induce ovulation. Treatment monitoring, oocyte retrieval and fertilisation techniques are performed according to the normal practice of the individual clinic.

Method of administration
Caution should be taken while inserting Zoladex into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.
Use extra care when administering Zoladex to patients with a low BMI and/or who are receiving full anticoagulation medication (see section 4.4).
For correct administration of Zoladex, see instructions on the instruction card.
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 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 Zoladex implant is visible. **(Figure 1).**

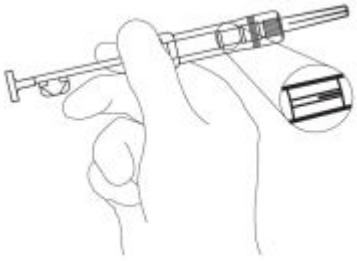

Figure 1.

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

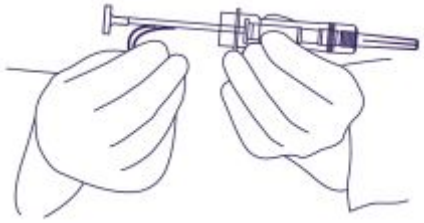

Figure 2.

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).**

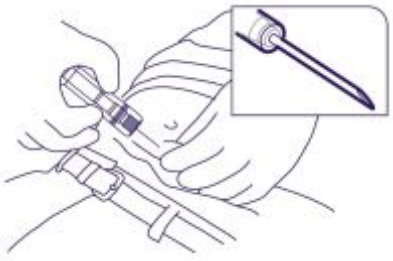

Figure 3.

NOTE: The 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 Zoladex implant may be injected with a new syringe elsewhere. Use extra care when administering 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 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 Zoladex implant, it may be localised by ultrasound.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as Goserelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Zoladex.

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 section 4.2).

Males
The use of 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. Consideration should be given to the initial use of an anti-androgen (e.g. cyproterone acetate 300 mg daily for 3 days before and 3 weeks after commencement of Zoladex) at the start of LHRH analogue therapy, since this has been reported to prevent the possible sequelae of the initial rise in serum testosterone. 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 reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with an LHRH agonist may reduce bone mineral loss.

Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with anticonvulsants or corticosteroids, family history of osteoporosis).

Patients with known depression and patients with hypertension should be monitored carefully.

Reduction in glucose tolerance has been observed in men receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in patients with pre-existing diabetes mellitus. Thus, monitoring of blood glucose levels should be considered.

Myocardial infarction and cardiac failure were 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.

Females

<u>Breast cancer indication</u>
Reduced bone mineral density:

The use of LHRH agonists may cause reduction in bone mineral density. Following two years treatment for early breast cancer, the average loss of bone mineral density 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% relative to baseline at the femoral neck and lumbar spine respectively, although this recovery is based on very limited data. In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of therapy.

Preliminary data suggest that the use of Zoladex in combination with tamoxifen in patients with breast cancer may reduce bone mineral loss.

<u>Benign indications</u>
Loss of bone mineral density:

The use of LHRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk. In the majority of women, currently available data suggest that recovery of bone loss occurs after cessation of therapy.

In patients receiving Zoladex for the treatment of endometriosis, the addition of hormone replacement therapy has been shown to reduce bone mineral density loss and vasomotor symptoms.

No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticosteroids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with Zoladex should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risks following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

Withdrawal bleeding
During early treatment with Zoladex some women may experience vaginal bleeding of variable duration and intensity. If vaginal bleeding occurs it is usually in the first month after starting treatment. Such bleeding probably represents oestrogen withdrawal bleeding and is expected to stop spontaneously. If bleeding continues, the reason should be investigated.

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.

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

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 Zoladex 3.6 mg, in combination with gonadotrophin. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. If OHSS risk is present, human chorionic gonadotrophin (hCG)should be withheld, if possible.

It is recommended that Zoladex 3.6 mg is used with caution in fertilisation treatment of patients with polycystic ovarian syndrome as follicle recruitment may be increased.

Fertile women should use non-hormonal contraceptive methods during treatment with Zoladex and until reset of menstruation following discontinuation of treatment with Zoladex.

Patients with known depression and patients with hypertension should be monitored carefully.

Treatment with Zoladex may lead to positive reactions in anti-doping tests.

Paediatric population
Zoladex 3.6 mg is not indicated for use in children, as safety and efficacy have not been established in this patient group.

4.5 Interaction with other medicinal products and other forms of interactions

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Zoladex with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Zoladex should not be used during pregnancy since concurrent use of LHRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentially fertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume (see also warning concerning the time to return of menses in section 4.4).

Pregnancy should be excluded before Zoladex 3.6 mg is used for fertilisation treatment. When Zoladex is used in this setting, there is no clinical evidence to suggest a causal connection between Zoladex and any subsequent abnormalities of oocyte development or pregnancy or outcome.

Breast-feeding

The use of Zoladex during breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Zoladex has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from Zoladex clinical trials and post-marketing sources. The most commonly observed adverse reactions include hot flushes, sweating and injection site reactions.

In this section undesirable effects are defined as follows:Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

Table: Zoladex 3.6 mg adverse drug reactions presented by MedDRA System Organ Class

SOC	Frequency	Males	Females
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour	Pituitary tumour
	Not known	N/A	Degeneration of uterine fibroid
Immune system disorders	Uncommon	Drug hypersensitivity	Drug hypersensitivity
	Rare	Anaphylactic reaction	Anaphylactic reaction
Endocrine disorders	Very rare	Pituitary haemorrhage	Pituitary haemorrhage
Metabolism and nutrition disorders	Common	Glucose tolerance impaired[a]	N/A
	Uncommon	N/A	Hypercalcaemia
Psychiatric disorders	Very common	Libido decreased[b]	Libido decreased[b]
	Common	Mood changes, depression	Mood changes, depression
	Very rare	Psychotic disorder	Psychotic disorder
Nervous system disorders	Common	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]	N/A
	Not known	QT prolongation (see sections	QT prolongation (see sections 4.4 and 4.5)

		4.4 and 4.5)	
Vascular disorders	Very common	Hot flush[b]	Hot flush[b]
	Common	Blood pressure abnormal[c]	Blood pressure abnormal[c]
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis[b]	Hyperhidrosis[b], acne[i]
	Common	Rash[d]	Rash[d], alopecia[g]
	Not known	Alopecia[h]	(see Common)
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]	N/A
		(see Uncommon)	Arthralgia
	Uncommon	Arthralgia	(see Common)
Renal and urinary disorders	Uncommon	Ureteric obstruction	N/A
Reproductive system and breast disorders	Very common	Erectile dysfunction	N/A
		N/A	Vulvovaginal dryness
		N/A	Breast enlargement
	Common	Gynaecomastia	N/A
	Uncommon	Breast tenderness	N/A
	Rare	N/A	Ovarian cyst
		N/A	Ovarian hyperstimulation syndrome (if used concomitantly with gonadotrophins)
	Not known	N/A	Withdrawal bleeding (see section 4.4)
General disorders and administration site conditions	Very common	(see Common)	Injection site reaction
	Common	Injection site reaction	(see Very common)
		N/A	Tumour flare, tumour pain (on initiation of treatment)
Investigations	Common	Bone density decreased (see section 4.4), weight increased	Bone density decreased (see section 4.4), weight increased

a. 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.

b. These are pharmacological effects which seldom require withdrawal of therapy. Hyperhidrosis and hot flushes may continue after stopping Zoladex.

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.

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

Post-marketing experience
A small number of cases of changes in blood count, hepatic dysfunction, pulmonary embolism and interstitial pneumonia have been reported in connection with Zoladex.
In addition, the following adverse drug reactions have been reported in women treated for benign gynaecological indications: Acne, change of body hairs, dry skin, weight gain, increase in serum cholesterol,ovarian hyperstimulation syndrome (if concomitantly used with gonadotropines), vaginitis, vaginal discharge, nervousness, sleep disorder, tiredness, peripheral oedema, myalgias, cramp in the calves, nausea, vomiting, diarrhoea, constipation, abdominal complaints, alterations of voice.

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

Rarely, breast cancer patients with metastases have developed hypercalcaemia on initiation of therapy. In the presence of symptoms indicative of hypercalcaemia (e.g. thirst), hypercalcaemia should be excluded.

Rarely, some women may enter the menopause during treatment with LHRH analogues and not resume menses on cessation of therapy. Whether this is an effect of Zoladex treatment or a reflection of their gynaecological condition is not known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

There is not much experience of overdose in humans. In cases where Zoladex has been given before the planned time of administration, or when a bigger dose of Zoladex than originally planned has been given, no clinically significant undesirable effects have been observed. 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. In case of overdosage, the condition should be managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin releasing hormone analogues,
ATC code: L02AE03.

Zoladex (D-Ser(Bu ^{t})^{6} Azgly^{10} LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration Zoladex results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum estradiol concentrations in females.

Initially, Zoladex like other LHRH agonists, transiently increases serum testosterone concentration in men and serum estradiol concentration in women. 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.

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

In women, serum estradiol concentrations are suppressed by around 21 days after the first depot injection and remain suppressed at levels comparable with those observed in postmenopausal women with continuous treatment every 28 days. This suppression is associated with endometrial thinning, suppression of follicular development within the ovary, a response in

hormone-dependent breast cancer (tumours that are ER-positive and/or PgR-positive), endometriosis and uterine fibroids and will result in amenorrhea 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 Zoladex is almost complete. Administration of a depot every four weeks ensures that effective concentrations are maintained with no accumulation. 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactide/glycolide 50/50 copolymer.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Zoladex 3.6 mg Implant is supplied as a single dose Safe System™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant. The syringe is moulded from polystyrene or styrene-butadiene copolymer and high density polyethylene.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1019/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd February 1989
Date of last renewal: 2nd February 2009

10 DATE OF REVISION OF THE TEXT

March 2019
CRN008M1K