Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zoladex LA 10.8mg Implant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Goserelin acetate equivalent to 10.8 mg goserelin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant.
A white to cream coloured, cylindrical depot in a pre-filled syringe

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

(i) Prostate cancer: Zoladex LA is indicated in the management of prostate cancer suitable for hormonal manipulation.
(ii) Endometriosis: Zoladex LA is indicated in the management of endometriosis including alleviation of symptoms, such as pain, and reduction in the size and number of endometrial lesions.
(iii) Uterine fibroids: Zoladex LA is indicated in the management of fibroids including shrinkage of lesions, improvement in the patient's haematological status and reduction of symptoms, such as pain. It can be used as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss.

4.2 Posology and method of administration

Posology

Adult men
One depot of Zoladex LA injected subcutaneously into the anterior abdominal wall every 3 months (see section 5.1 Pharmacodynamic properties).

Adult Women
Endometriosis and Uterine Fibroids: Treatment is for a period of six months only as there are no clinical data to justify longer treatment periods. Repeat courses should not be given due to the concern about loss in bone mineral density. In patients receiving Zoladex 3.6 mg for the treatment of endometriosis, the addition of hormone replacement therapy (a daily oestrogenic agent and progestrogenic agent) has been shown to reduce bone mineral density loss and vasomotor symptoms. There is no experience of the use of hormone replacement therapy in women receiving Zoladex LA.

Elderly
No dosage adjustment is necessary in the elderly.

Renal impairment
No dosage adjustment is necessary for patients with renal impairment, but half-life is increased in patients with impaired renal function.

Hepatic impairment
No dosage adjustment for patients with hepatic impairment.

Paediatric population
Zoladex LA is not indicated for use in children.

Method of administration

Caution should be taken while inserting Zoladex LA into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

Use extra care when administering Zoladex LA to patients with a low BMI and/or who are receiving full anticoagulation medication (see section 4.4).

For correct administration of Zoladex LA, see instructions on the pouch/carton.

Zoladex LA 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 LA 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 LA implant is visible. **(Figure 1).**

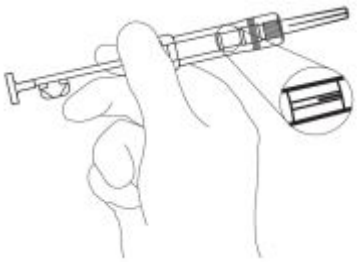

Figure 1.

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 LA implant.**

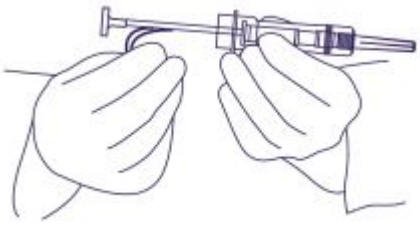

Figure 2.

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).**

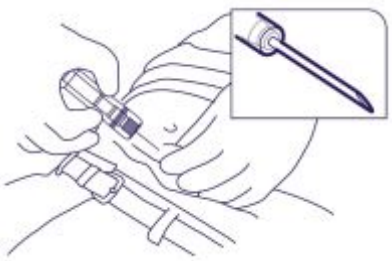

Figure 3.

NOTE: The Zoladex LA 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 LA implant may be injected with a new syringe elsewhere. Use extra care when administering Zoladex LA 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 LA 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 LA 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 no data on removal or dissolution of the implant.

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 LA.

Injection site injury has been reported with Zoladex LA, 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 LA to patients with a low BMI and/or receiving full anticoagulation medications (see section 4.2).

Males
The use of Zoladex LA 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.

Consideration should be given to the initial use of an anti-androgen (e.g. cyproterone acetate 300 mg daily for three days before and three 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.

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
In women, Zoladex LA is indicated only for the treatment of endometriosis and fibroids. For female patients who need goserelin treatment for other indications, see the prescribing information for Zoladex 3.6 mg.

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 (HRT) has been shown to reduce bone mineral density loss and vasomotor symptoms. There is no experience of the use of HRT in women receiving Zoladex LA.

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.

Time to return of menses after cessation of therapy with Zoladex LA may be prolonged in some patients (the mean duration of secondary amenorrhoea after cessation of use of Zoladex LA is 7-8 months). If quick return of menses is important, Zoladex 3.6 mg is recommended.

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.

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 LA 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 LA 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 LA 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).

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

4.7 Effects on ability to drive and use machines

Zoladex LA 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 LA adverse drug reactions presented by MedDRA System Organ Class

SOC	**Frequency**	**Males**	**Females**
Neoplasms benign, malignant and unspecified (including cysts and	Very rare	Pituitary	Pituitary

polyps)		tumour	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
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 4.4 and 4.5)	QT prolongation (see sections 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
	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.
A small number of cases of hypercalcaemia have been reported in women being treated for endometriosis and/or fibroids. In the presence of symptoms 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 LA. 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 luteinising-hormone releasing hormone (LHRH). On chronic administration Zoladex LA results in inhibition of pituitary luteinising hormone secretion leading to a fall in serum testosterone concentrations in men and serum estradiol concentrations in women. Initially Zoladex LA like other LHRH agonists transiently increases serum testosterone concentrations in men and serum estradiol 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 estradiol 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 estradiol already suppressed by an LHRH analogue, suppression is maintained on the change of therapy to Zoladex LA. Suppression of estradiol 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.

5.2 Pharmacokinetic properties

Administration of Zoladex LA in accordance with the dosing 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 two to four hours in subjects with normal renal function. Maximum serum concentrations (mean C_{max} = 8-10 mg/ml) were achieved after a single administration of 10.8mg Zoladex after approximately 2 hours. After 24 hours goserelin will decline rapidly up to Day 4. Thereafter, mean concentration remains relatively stable in the range of about 0.3 to 1ng/ml up to the end of the treatment period. The half-life is increased in patients with impaired renal function. For the compound given, as recommended, in a 10.8mg 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.

5.3 Preclinical safety data

Following long-term repeated dosing with Zoladex LA, 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. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactide/glycolide 95/5 copolymer Low Molecular Weight.
Lactide/glycolide 95/5 copolymer High Molecular Weight.

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 LA 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

PA1019/027/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd January 1996

Date of last renewal: 2nd February 2009

10 DATE OF REVISION OF THE TEXT

March 2019
CRN008M1K