ZOLADEX® LA 10.8 MG
(*goserelin*)

1. Name of the medicinal product
Zoladex LA 10.8 mg depot

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
Depot, pre-filled syringe

4. Clinical Particulars
4.1 Indications
Prostate cancer: Zoladex LA 10.8 mg is indicated in the management of prostate cancer suitable for hormonal manipulation.

Premenopausal Breast cancer: Zoladex LA 10.8mg is indicated in the management of estrogen-receptor-positive breast cancer in premenopausal women.

Endometriosis: In the management of endometriosis, Zoladex LA 10.8mg alleviates symptoms, including pain, and reduces the size and number of endometrial lesions.

4.2 Dosage and administration
Posology
Adult Males (including older people): One 10.8 mg depot of Zoladex LA injected subcutaneously into the anterior abdominal wall, every 12 weeks.

Adult Females: One 10.8 mg depot of Zoladex LA injected subcutaneously into the anterior abdominal wall, every 12 weeks.

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

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

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

Method of administration
For correct administration of Zoladex, see instructions on the instruction card.

The instruction card has to be read prior to administration.
Caution is needed when administering Zoladex LA into anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

Extra care to be given to patients with a low BMI or who are receiving anticoagulation medication (see section 4.4).

Care should be taken to ensure injection is given subcutaneously, using the technique described in the instruction card. Do not penetrate into a blood vessel, muscle or peritoneum.

In the event of the need to surgically remove a Zoladex LA implant, it may be localised by ultrasound.

For special precautions for disposal and other handling see section 6.7.

Children
Zoladex LA 10.8 mg is not indicated for use in children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Warnings and Precautions

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 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 developed, 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.

Myocardial infarction and cardiac failure were observed in a pharmacoepidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.

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 blood glucose levels should be considered.

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

Females

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

In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority. In patients receiving Zoladex 3.6mg 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 LA 10.8mg.

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.

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 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 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 resume. (Also see the warning relating to return of menses in Section 4.4.)

Lactation: The use of Zoladex 10.8 mg during breast feeding is not recommended.

4.7 Effect on ability to drive or operate machinery

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

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.

The following convention has been used for classification of frequency: 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 1 Zoladex LA adverse drug reactions by frequency and System Organ Class (SOC)

SOC	Frequency	Male	Females
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour	Pituitary tumour
	Not known		Degenerative 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]	Glucose tolerance impaired[a]
	Uncommon		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 Spinal cord compression	Paraesthesia Headache
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]	
	Not known	QT prolongation (see sections 4.4 and 4.5)	QT prolongation
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[h]
	Not Known	Alopecia[h]	
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]	Bone pain[e], Arthralgia
	Uncommon	Arthralgia	
Renal and urinary disorders	Uncommon	Ureteric obstruction	
Reproductive system and breast disorders	Very common	Erectile dysfunction	Vulvovaginal dryness, Breast enlargement
	Common	Gynaecomastia	
	Uncommon	Breast tenderness	
	Rare		Ovarian cyst
	Not known		Withdrawal bledding
General disorders and administration site conditions	Very common		Injection site reaction
	Common	Injection site reaction	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 Particularly loss of body hair, an expected effect of lowered androgen levels.
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.

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.

4.9 Overdosage

There is not much experience of overdosage 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 10.8 mg. In case of overdosage, this condition should be managed symptomatically.

5 Pharmaceutical Particulars

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Gonadotropin 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 LH secretion leading to a fall in serum testosterone concentrations in men and serum oestradiol concentrations in women. Initially, Zoladex LA, like other LHRH agonists, may transiently increases serum testosterone concentration in men and serum oestradiol concentration 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 12 weeks.

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 at levels comparable with those observed in postmenopausal women. Suppression of oestradiol is associated with a response in breast cancer in premenopausal women 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.

Prostate cancer

In the management of patients with metastatic prostate cancer, Zoladex has been shown in comparative clinical trials to give similar survival outcomes to those obtained with surgical castrations.

In a combined analysis of 2 randomised controlled trials comparing bicalutamide 150 mg monotherapy versus castration (predominantly in the form of Zoladex), there was no significant difference in overall survival between bicalutamide-treated patients and castration-treated patients (hazard ratio = 1.05 [CI 0.81 to 1.36]) with locally advanced prostate cancer. However, equivalence of the two treatments could not be concluded statistically.

In comparative trials, Zoladex has been shown to improve disease-free survival and overall survival when used as an adjuvant therapy to radiotherapy in patients with high-risk localised (T_1-T_2 and PSA of at least 10 ng/mL or a Gleason score of at least 7), or locally advanced (T_3-T_4) prostate cancer. The optimum duration of adjuvant therapy has

not been established; a comparative trial has shown that 3 years of adjuvant Zoladex gives significant survival improvement compared with radiotherapy alone. Neo-adjuvant Zoladex prior to radiotherapy has been shown to improve disease-free survival in patients with high risk localised or locally advanced prostate cancer.

After prostatectomy, in patients found to have extra-prostatic tumour spread, adjuvant Zoladex may improve disease-free survival periods, but there is no significant survival improvement unless patients have evidence of nodal involvement at time of surgery. Patients with pathologically staged locally advanced disease should have additional risk factors such as PSA of at least 10 ng/mL or a Gleason score of at least 7 before adjuvant Zoladex should be considered. There is no evidence of improved clinical outcomes with use of neoadjuvant Zoladex before radical prostatectomy.

Breast Cancer

Japanese Phase II study

Disease free survival following subcutaneous administration of Zoladex LA 10.8mg once every 12 weeks as adjuvant therapy to premenopausal women with estrogen-receptor-positive breast cancer who underwent radical surgery was assessed in comparison with Zoladex 3.6 mg, both in combination with tamoxifen citrate (the duration of treatment was 96 weeks). Four (4.7%) and 1 (1.2%) events were observed in the Zoladex LA 10.8mg group and Zoladex 3.6 mg group, respectively, with median (min, max) disease free survival of 675.0 days (142 days, 687 days) and 675.5 days (160 days, 685 days) in the Zoladex LA 10.8mg group and Zoladex 3.6 mg group, respectively.

Asian multinational Phase III study

The efficacy and safety of subcutaneous administration of Zoladex LA 10.8mg once every 12 weeks to premenopausal women with estrogen-receptor-positive advanced/recurrent breast cancer were assessed in comparison with Zoladex 3.6 mg, both in combination with tamoxifen citrate (the duration of treatment was 24 weeks). The proportion of patients with progression free survival (%PFS) at Week 24, the primary endpoint, were 67/109 (61.5%) in the Zoladex LA 10.8mg and 68/113 (60.2%) in the Zoladex 3.6 mg with the difference [95% CI] of 1.29% [-11.40 - 13.90], which met the pre-specified non-inferiority criterion.

5.2 Pharmacokinetic Properties

Administration of Zoladex LA every 12 weeks 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. The half-life is increased in patients with impaired renal function. For the compound given in a 10.8 mg depot formulation every 12 weeks, 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.

Following subcutaneous administration of this drug to premenopausal patients with breast cancer, plasma goserelin concentrations reached Cmax 2 hours at-post dose (mean value of 4.5 ng/mL). Subsequently, plasma goserelin levels decreased promptly until 48 hours postdose, and thereafter it eliminated gradually and maintained around the lower limit of quantitation (0.1 ng/mL) at Week 10 and 12.

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.

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

A blend of high and low molecular weight lactide/glycolide copolymers

6.2 Incompatibilities

None known

6.3 Shelf-life

Please refer to expiry date on outer carton

6.4. Pack size

One syringe.

6.5 Special precautions for storage

Store below 30°C.

6.6 Nature and contents of container

Zoladex LA is supplied as a single dose SafeSystem™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant.

6.7 Special precautions for disposal and other handling

Use as directed by the prescriber. Use only if pouch is undamaged. Use immediately after opening pouch. Dispose of the syringe in an approved sharps collector.

Date of revision of the text

September 2023
Doc ID-002717344 V9

Instructions for inclusion on the instruction card as applicable:

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

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).**

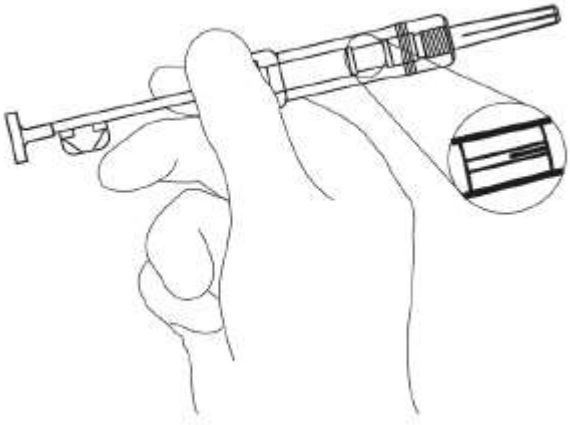

Figure 1

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.**

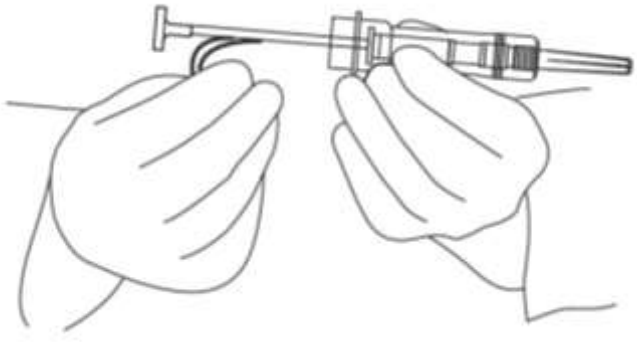

Figure 2

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).**

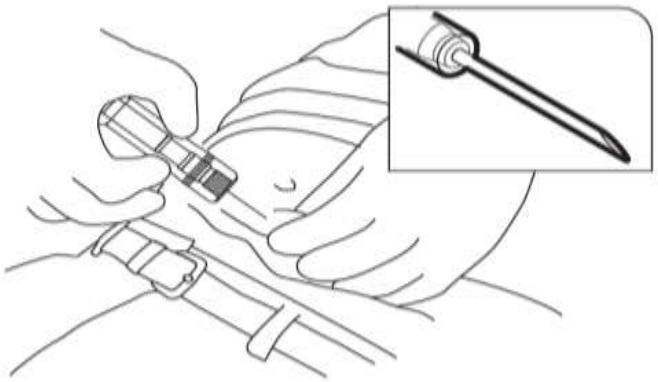

Figure 3

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.

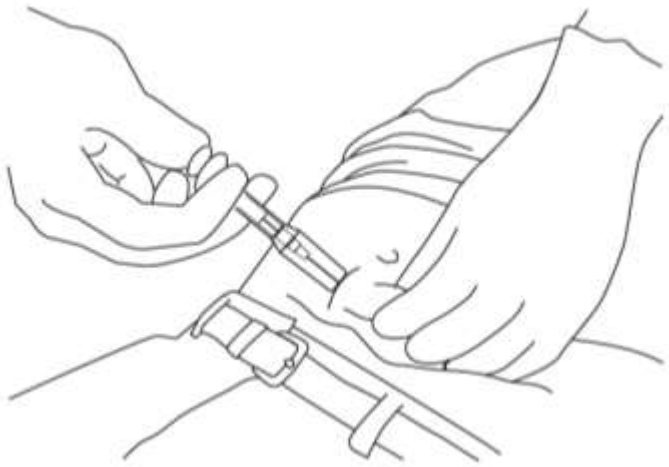

Figure 5

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