Certificate Number: PP10163196

SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

Zoladex LA 10.8 mg 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, in pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zoladex is indicated (see also section 5.1):

- In the treatment of metastatic prostate cancer where Zoladex has demonstrated comparable survival benefits to surgical castrations (see section 5.1)
- In the treatment of locally advanced prostate cancer, as an alternative to surgical castration where Zoladex has demonstrated comparable survival benefits to an anti-androgen (see section 5.1)
- As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival and overall survival (see section 5.1)
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival (see section 5.1)
- As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression where Zoladex has demonstrated improved disease-free survival (see section 5.1)

4.2 Posology and method of administration

Posology

Adult males (including the elderly): one 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 for patients with hepatic impairment.

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

Method of administration

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

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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 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Zoladex LA is not indicated for use in females, since there is insufficient evidence of reliable suppression of serum estradiol. For female patients requiring treatment with goserelin, refer to the prescribing information for Zoladex 3.6 mg.

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.

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 develop, specific standard treatment of these complications should be instituted.

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).

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 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.

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.

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 interaction
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
Zoladex LA is not indicated for use in females.

4.7 Effects on ability to drive and use machines
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).

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

SOC	Frequency	Adverse reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour
Immune system disorders	Uncommon	Drug hypersensitivity
	Rare	Anaphylactic reaction
Endocrine disorders	Very rare	Pituitary haemorrhage
Metabolism and nutrition disorders	Common	Glucose tolerance impaired[a]
Psychiatric disorders	Very common	Libido decreased[b]
	Common	Mood changes, depression
	Very rare	Psychotic disorder
Nervous system disorders	Common	Paraesthesia
		Spinal cord compression
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]
	Not known	QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common	Hot flush[b]
	Common	Blood pressure abnormal[c]
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis[b]
	Common	Rash[d]
	Not known	Alopecia[g]
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]
	Uncommon	Arthralgia
Renal and urinary disorders	Uncommon	Ureteric obstruction
Reproductive system and breast disorders	Very common	Erectile dysfunction
	Common	Gynaecomastia
	Uncommon	Breast tenderness
General disorders and administration site conditions	Common	Injection site reaction
Investigations	Common	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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

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

Pharmacotherapuetic 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 luteinising hormone secretion leading to a fall in serum testosterone concentrations in males. Initially, Zoladex LA like other LHRH agonists transiently increases serum testosterone concentrations.

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 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.

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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 neo-adjuvant Zoladex before radical prostatectomy.

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.

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

36 months.

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 SafeSystem™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant.

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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. Dispose of the syringe in an approved sharps collector.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,

600 Capability Green,

Luton,

LU1 3LU,

UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17901/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st May 2001

Date of latest renewal: 4th June 2008

10 DATE OF REVISION OF THE TEXT

24/01/2017