

Summary of Product Characteristics

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 a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant.

Product imported from the UK:

White to cream-coloured, cylindrical implant 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

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 3.6mg for the treatment of endometriosis, the addition of hormone replacement therapy (a daily oestrogenic agent and progestogenic 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.

Children - Zoladex LA is not indicated for use in children.

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.

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

4.3 Contraindications

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

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

There is no data on removal or dissolution of the implant.

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).

Mood changes, including depression have been reported. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Not known

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).

Lactation

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

4.7 Effects on ability to drive and use machines

There is no evidence that Zoladex LA would result in impairment of ability to drive or operate machinery.

4.8 Undesirable effects

The following frequency categories were based on all adverse reactions from clinical trials, post-marketing studies and spontaneous reports. 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ 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
Neoplasm benign and malignant (including cysts and polyps)	Very rare	Pituitary tumour	Pituitary tumour
	Not known	N/A	Degeneration of uterine fibroids in women with uterine fibroids
Immune system disorders	Uncommon	Hypersensitivity reactions	Hypersensitivity reactions
	Rare	Anaphylaxis	Anaphylaxis
Endocrine disorders	Very rare	Pituitary apoplexy	Pituitary apoplexy
Metabolism and nutrition disorders	Common	Reduction in glucose tolerance ^a	N/A
Psychiatric disorders	Very common	Change in libido ^b	Change in libido ^b
	Common	(see Not known)	Mood changes, including depression
	Very rare	Psychotic disorders	Psychotic disorders
	Not known	Mood changes, including depression	(see Common)
Nervous system disorders	Common	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
Vascular disorders	Very common	Hot flushes ^b	Hot flushes ^b
	Common	Fluctuations in blood pressure ^c	Fluctuations in blood pressure ^c
Skin and subcutaneous tissue disorders	Very common	Sweating ^b	Sweating ^b
	Common	Rash ^d	Rash ^d
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	Decrease in potency	N/A
		N/A	Vaginal dryness
		N/A	Change in breast size
	Common	Breast swelling	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 reactions (e.g. redness, pain, swelling, haemorrhage)
	Common	Injection site reactions (e.g. redness, pain, swelling, haemorrhage)	(see Very common)

Investigations	Common	Bone mineral density loss (see section 4.4)	Bone mineral density loss (see section 4.4)
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- 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.
- 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.

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.

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

Zoladex (D-Ser(Bu^t)⁶ Azgly¹⁰ 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

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

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the pouch, syringe and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

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.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Use as directed by the prescriber. Use only if pouch is undamaged. Use immediately after opening pouch. Any unused product, syringes or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
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Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/61/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th of August 2010

10 DATE OF REVISION OF THE TEXT

March 2011