PACKAGE LEAFLET TEXT

ZOLADEX 3.6mg

(goserelin)

~~**Presentation**~~

~~'Zoladex' is presented as a sterile, white to cream coloured cylindrical depot in which goserelin acetate (equivalent to 3.6 mg of goserelin) is dispersed in a biodegradable matrix of lactide-glycolide co-polymer. It is supplied as a single dose SafeSystem™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant.~~

Name of the medicinal product

Zoladex 3.6mg

Qualitative and quantitative composition

Goserelin acetate (equivalent to 3.6 mg goserelin)

Pharmaceutical form

Depot, pre-filled syringe.

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 premenopausal 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) Endometrial thinning: Zoladex 3.6mg is indicated for the prethinning of the uterine endometrium prior to endometrial ablation or resection.

v) Uterine fibroids: 'In conjunction with iron therapy in the haematological improvement of anaemic patients with fibroids, prior to surgery.

vi) Assisted reproduction: Pituitary downregulation in preparation for superovulation.

Dosage and administration

Adults

One 3.6 mg depot of Zoladex injected subcutaneously into the anterior abdominal wall, every 28 days.

Assisted reproduction: Zoladex 3.6mg is administered to downregulate the pituitary gland, as defined by serum oestradiol levels similar to those observed in the early follicular phase (approximately 150 pmol/1). 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.

No dosage adjustment is necessary for patients with renal impairment.

No dosage adjustment is necessary for patients with hepatic impairment.

No dosage adjustment is necessary in the elderly.

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

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 density loss and vasomotor symptoms.

For use in endometrial thinning; two depots to be administered 4 weeks apart, with surgery timed for between zero and two weeks after the second depot.

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

Children

Zoladex 3.6mg is not indicated for use in children.

For correct administration of Zoladex 3.6mg, see instructions on the instruction card.

Contra-indications

Zoladex 3.6mg should not be given to patients with a known hypersensitivity to the active substance, to other LHRH analogues, or to any excipients of this product.

Zoladex 3.6mg should not be used during pregnancy or lactation.

Warning and precautions

Zoladex 3.6mg is not indicated for use in children as safety and efficacy have not been established in this group of patients.

~~Males~~

The use of Zoladex 3.6mg 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.

~~Females~~

The use of LHRH agonists ~~in women~~ may cause a ~~loss of~~ reduction in bone mineral density. Currently available Zoladex 3.6mg data indicate a mean loss of 4.6% in vertebral bone mineral density following a six month course of treatment with progressive recovery to a mean loss compared to baseline of 2.6% six months after cessation of treatment. 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 density loss and vasomotor symptoms. In men, preliminary data suggest the use of a bisphosphonate in combination with an LHRH agonist may reduce bone mineral loss.

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. Consideration should therefore be given to monitoring blood glucose.

Zoladex 3.6mg should be used with caution in women with known metabolic bone disease.

Zoladex 3.6mg may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix.

Currently, there are no clinical data on the effects of treating benign gynaecological conditions with Zoladex 3.6mg for periods in excess of six months.

Assisted Reproduction:

Zoladex 3.6mg 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 3.6mg, in combination with gonadotrophin. It has been suggested that the downregulation achieved with a depot

agonist may lead, in some cases, to an increased requirement for gonadotrophin. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS because its severity and incidence may be dependent on the dose regimen of gonadotrophin. Human chorionic gonadotrophin (hCG) should be withheld, if appropriate.

It is recommended that Zoladex 3.6mg be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome as follicle recruitment may be increased.

Interactions

None known

Pregnancy and lactation

Although reproductive toxicology in animals gave no evidence of teratogenic potential, Zoladex 3.6mg 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 and in the case of endometriosis until menses are resumed.

Pregnancy should be excluded before Zoladex 3.6mg is used for assisted reproduction. The clinical data from use in this setting are limited but the available evidence suggests there is no causal association between Zoladex 3.6mg and any subsequent abnormalities of oocyte development or pregnancy and outcome.

The use of Zoladex 3.6mg during breast feeding is not recommended.

Effect on ability to drive or operate machinery

There is no evidence that Zoladex 3.6mg results in impairment of these activities.

Undesirable effects

~~General~~

Rare incidences of hypersensitivity reactions, which may include some manifestations of anaphylaxis, have been reported.

Arthralgia has been reported. Non-specific paraesthesias have been reported. Skin rashes have been reported which are generally mild, often regressing without discontinuation of therapy.

Changes in blood pressure, manifest as hypotension or hypertension, have been occasionally observed in patients administered Zoladex 3.6mg. The changes are usually transient, resolving either during continued therapy, or after cessation of therapy with Zoladex 3.6mg. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of Zoladex 3.6mg treatment.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration.

Occasional local reactions include mild bruising at the subcutaneous injection site.

~~Males~~

Pharmacological effects in men include hot flushes and sweating and a decrease in potency, seldom requiring withdrawal of therapy. Breast swelling and tenderness have been noted infrequently. Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically. Isolated cases of ureteric obstruction and spinal cord compression have been recorded.

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.

The use of LHRH agonists ~~in men~~ may cause a ~~loss of~~ reduction in bone mineral density.

~~Females~~

Pharmacological effects in women include hot flushes and sweating, and a change in libido, seldom requiring withdrawal of therapy. Headaches, mood changes including depression, vaginal dryness and change in breast size have been noted infrequently. Initially breast cancer patients may experience a temporary increase in signs and symptoms, which can be managed symptomatically. In women with fibroids, degeneration of fibroids may occur. Rarely, breast cancer patients with bony metastases have developed hypercalcaemia on initiation of therapy.

In Assisted Reproduction: As with other LHRH agonists, there have been reports of ovarian hyperstimulation syndrome (OHSS), associated with the use of Zoladex 3.6mg in combination with gonadotrophin. It has been suggested that the downregulation achieved with a depot agonist may lead, in some cases, to an increased requirement for gonadotrophin. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS because its severity and incidence may be dependent on the dose regimen of gonadotrophin. Human chorionic gonadotrophin (hCG) should be withheld, if appropriate.

Follicular and luteal ovarian cysts have been reported to occur following LHRH therapy. Most cysts are asymptomatic, non functional, varying in size and resolve spontaneously.

Overdosage

There is limited experience of overdosage in humans. In cases where Zoladex 3.6mg has unintentionally been readministered early, or given at a higher dose, no clinically relevant adverse effects have been seen. 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 3.6mg. If overdosage occurs, this should be managed symptomatically.

~~**Pharmacological properties**~~

Pharmacodynamic properties

Mode of action: Zoladex 3.6mg (D-Ser(Bu^t)^6 $Azgly^{10}$ LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration Zoladex 3.6mg results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum oestradiol concentrations in females. This effect is reversible on discontinuation of therapy. Initially, Zoladex 3.6mg, like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum oestradiol concentration in women. During early treatment with Zoladex 3.6mg 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 oestradiol concentrations are suppressed by around 21 days after the first depot injection and, with continuous treatment every 28 days, remain suppressed at levels comparable with those observed in postmenopausal women. This suppression is associated with a response in hormone dependent breast cancer, endometriosis, uterine fibroids and suppression of follicular development within the ovary. It will produce endometrial thinning and will result in amenorrhoea in the majority of patients.

Zoladex 3.6mg in combination with iron has been shown to induce amenorrhoea and improve haemoglobin concentrations and related haematological parameters in women with fibroids who are anaemic. The combination produced a mean haemoglobin concentration 1g/dl above that achieved by iron therapy alone.

During treatment with LHRH analogues patients may enter the menopause. Rarely, some women do not resume menses on cessation of therapy.

Pharmacokinetic properties

The bioavailability of Zoladex 3.6mg is almost complete. Administration of a depot every four weeks ensures that effective concentrations are maintained with no tissue accumulation. Zoladex 3.6mg 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.

Preclinical safety data

Following long-term repeated dosing with Zoladex 3.6mg, 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 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.

Precautions for storage

Do not store above 25°C

Instructions for use, handling and disposal

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.

Pack size

Please refer to the outer carton for pack size.

Shelf life

Please refer to expiry date on outer carton.

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