P041124

ZOLADEX 3.6 mg

(goserelin)

Name of the medicinal product
ZOLADEX 3.6 mg

Qualitative and quantitative composition
Goserelin acetate (equivalent to 3.6 mg goserelin)

Pharmaceutical form
Depot, pre-filled syringe.

Indications

i) Prostate cancer: ZOLADEX 3.6 mg is indicated in the management of prostate cancer suitable for hormonal manipulation.

ii) Breast cancer: ZOLADEX 3.6 mg 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 3.6 mg alleviates symptoms, including pain, and reduces the size and number of endometrial lesions.

iv) Endometrial thinning: ZOLADEX 3.6 mg 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
Caution should be taken while inserting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

Use extra care when administering ZOLADEX to patients with a low BMI and/or who are receiving full anticoagulation medication [see Warnings and precautions].

For correct administration of ZOLADEX, see instructions on the instruction card (see Instructions for use, handling and disposal).

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

Assisted reproduction: ZOLADEX 3.6 mg 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/l). 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 3.6 mg 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 3.6 mg depot with supplementary iron may be given for up to three months before surgery.

Children
ZOLADEX 3.6 mg is not indicated for use in children.

Contra-indications
ZOLADEX 3.6 mg 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 3.6 mg should not be used during pregnancy or lactation.

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

Injection site injury has been reported with ZOLADEX, 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 to patients with a low BMI and/or receiving full anticoagulation medications [see Dosage and administration].

The use of ZOLADEX 3.6 mg 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.
The use of LHRH agonists may cause a reduction in bone mineral density. Currently available ZOLADEX 3.6 mg 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 3.6 mg 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 3.6 mg should be used with caution in women with known metabolic bone disease.

ZOLADEX 3.6 mg 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 3.6 mg for periods in excess of six months.

Androgen deprivation therapy may prolong the QT interval, although a causal association has not been established with ZOLADEX. In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may prolong the QT interval (see Interactions) physicians should assess the benefit risk ratio including the potential for Torsade de Pointes prior to initiating ZOLADEX.

Assisted Reproduction:
ZOLADEX 3.6 mg 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 3.6 mg, 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 3.6 mg be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome as follicle recruitment may be increased.

Interactions
None known

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ZOLADEX with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de Pointes should be carefully evaluated (see Warnings and precautions).

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

Pregnancy should be excluded before ZOLADEX 3.6 mg 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 3.6 mg and any subsequent abnormalities of oocyte development or pregnancy and outcome.

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

Effect on ability to drive or operate machinery
There is no evidence that ZOLADEX 3.6 mg results in impairment of ability to drive or operate machinery.

Undesirable effects
The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from ZOLADEX clinical trials and post-marketing sources.

Area for text

Edge code area

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Perigord Job No.:	262122 Artworker Initials: VA
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Version No.:	01
Date & Time:	28 August 2015 11:42
Ops Component Code:	P041124
Drawing Ref:	630170L4
Pack Line Code Data:	5120
Description:	Zoladex Leaflet

Printable Colours: Black

Non Print: Profile, Technical Info

Perigord premedia

Bar prints 100mm @ 100%

Font information
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Smallest text size: 7.0 pt (excluding component code)
Condensed Fonts Used: N

Drawing Ref: 630170L4
Dimensions (mm):
Length: 630.00
Width: 170.00
Version: 3 - 01.12.2014
Created by: JH
Ops site: Macclesfield

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Table 1 ZOLADEX 3.6 mg adverse drug reactions by frequency and System Organ Class (SOC)

Frequency Descriptor	SOC	Males	Females
Very Common (≥10%)	Psychiatric disorders	Libido decreased[b]	Libido decreased[b]
	Vascular disorders	Hot flush[a]	Hot flush[a]
	Skin and subcutaneous tissue disorders	Hyperhidrosis[a]	Hyperhidrosis[a], acne[j]
	Reproductive system and breast disorders	Erectile dysfunction	N/A
		N/A	Vulvovaginal dryness
		N/A	Breast enlargement
	General disorders and administration site conditions	(see Common)	Injection site reactions
Common (≥1%and <10%)	Metabolism and nutrition disorders	Glucose tolerance impaired[b]	NA
	Psychiatric disorders	Mood swings	Mood altered, depression
	Nervous system disorders	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
	Cardiac disorders	Cardiac failure[f], myocardial infarction[f]	N/A
	Vascular disorders	Blood pressure abnormal[c]	Blood pressure abnormal[c]
	Skin and subcutaneous tissue disorders	Rash[d]	Rash[d]
		(see unknown)	Alopecia[g]
	Musculoskeletal, connective tissue and bone disorders	Bone pain[e]	N/A
		(see Uncommon)	Arthralgia
	Reproductive system and breast disorders	Gynaecomastia	N/A
	General disorders and administration site conditions	N/A	Tumour flare, tumour pain
		Injection site reaction	(see Very common)
	Investigations	Bone density decreased	Bone density decreased
		Weight increased	Weight increased
Uncommon (≥0.1% and <1%)	Immune system disorders	Drug hypersensitivity	Drug hypersensitivity
	Musculoskeletal, connective tissue and bone disorders	Arthralgia	(see Common)
	Renal and urinary disorders	Ureteric obstruction	N/A
	Reproductive system and breast disorders	Breast tenderness	N/A
	Metabolism and nutrition disorders	N/A	Hypercalcaemia
Rare (≥0.01% and <0.1%)	Immune system disorders	Anaphylactic reaction	Anaphylactic reaction
Rare (continued)	Reproductive system and breast disorders	N/A	Ovarian cyst
		N/A	Ovarian hyperstimulation syndrome
Very rare (<0.01%)	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pituitary tumour	Pituitary tumour
	Endocrine disorders	Pituitary haemorrhage	Pituitary haemorrhage
	Psychiatric disorders	Psychotic disorder	Psychotic disorder
Unknown	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N/A	Degeneration of uterine fibroid
	Skin and subcutaneous tissue disorder	Alopecia[a]	(see common)
	Cardiac disorders	QT prolongation	QT prolongation

[a] These are pharmacological effects which seldom require withdrawal of therapy.
[b] 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.
[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 can occasionally be severe.
[h] Particularly loss of body hair, an expected effect of lowered androgen levels.
[j] In most cases acne was reported within one month after the start of ZOLADEX.

Overdosage

There is limited experience of overdosage in humans. In cases where ZOLADEX 3.6 mg 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 3.6 mg. If overdosage occurs, this should be managed symptomatically.

Pharmacodynamic properties

Mode of action: ZOLADEX 3.6 mg (D-Ser(But)^{6} Azgly^{10} LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration ZOLADEX 3.6 mg 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 3.6 mg, like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum oestradiol concentration in women. During early treatment with ZOLADEX 3.6 mg 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 3.6 mg 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 3.6 mg is almost complete. Administration of a depot every four weeks ensures that effective concentrations are maintained with no tissue accumulation. ZOLADEX 3.6 mg 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 3.6 mg, 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

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

Use as directed by the prescriber. Use extra care when administering ZOLADEX to patients with a low BMI and/or who are receiving full anticoagulation medication [see Warnings and precautions].

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.

Date of revision of text

July 2015

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AstraZeneca UK Limited, Macclesfield, Cheshire, England.

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Perigord Job No.: 262122 Artworker Initials: VA
Market: Standard English
Version No.: 01
Date & Time: 28 August 2015 11:42
Ops Component Code: P041124
Drawing Ref: 630170L4
Pack Line Code Data: 5120
Description: Zoladex Leaflet

Printable Colours: Black

Non Print: Profile, Technical Info

Perigord premedia

Bar prints 100mm @ 100%

Font information
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Smallest text size: 7.0 pt (excluding component code)
Condensed Fonts Used: N