Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Zoladex® 10,8 mg, Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZOLADEX 10,8 mg pre-filled syringe contains goserelin acetate equivalent to 10,8 mg goserelin base.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

White to cream coloured cylindrical pieces of rigid polymeric material, free or practically free from visible impurities. The depot is supplied in a pre-loaded single-dose disposable syringe applicator.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Males

Prostate cancer:

ZOLADEX 10,8 mg is indicated in the management of prostate cancer suitable for hormonal manipulation.

Females

Endometriosis:

Relief of clinical symptoms associated with endometriosis.

Uterine fibroids:

Reduction of uterine fibroid size before surgery.

Breast cancer:

ZOLADEX 10.8 mg is indicated in the management of oestrogen-receptor-positive breast cancer in premenopausal women.

ZOLADEX should not be used for more than 6 months for gynaecological indications in women due to its effects on bone metabolism (see section 4.4).

4.2. Posology and method of administration

Adult men, including the elderly: One ZOLADEX 10,8 mg injected subcutaneously into the anterior abdominal wall, every 3 months (see section 5.1).

Adult women: One ZOLADEX 10,8 mg injected subcutaneously into the anterior abdominal wall, every 12 weeks.

No dosage adjustment is necessary for patients with renal impairment, hepatic impairment, nor for the elderly.

For correct administration of ZOLADEX, see instructions on the carton.

Children:

ZOLADEX 10,8 mg is not for use in children. (See section 4.3).

4.3. Contraindications

Known severe hypersensitivity to the active substance or to any of the excipients of ZOLADEX 10,8 mg.

Pregnancy and lactation (see section 4.6).

Children:

ZOLADEX is not indicated for use in children (see section 4.2).

4.4.Special warnings and precautions for use

Patients with proven non-hormone dependent cancer e.g. those who have failed to respond to previous surgical castration or oestrogens, are less likely to respond to ZOLADEX than previously untreated patients.

The use of ZOLADEX 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.

ZOLADEX may cause an increase in uterine cervical resistance, which may result in difficulty when the cervix is dilated. Care should be taken when dilating the cervix.

The safety and efficacy of ZOLADEX for gynaecological conditions have not been established for periods exceeding 6 months (see section 4.4).

The use of ZOLADEX may cause a reduction in bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority. In women 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. There is no experience of the use of hormone replacement therapy in women receiving ZOLADEX 10,8 mg. 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 such as ZOLADEX. 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.

Time to return of menses after cessation of therapy with ZOLADEX 10,8 mg may be prolonged.

Following long-term repeated dosing with ZOLADEX, an increased incidence of benign pituitary tumours have been observed in male rats. Whilst this finding is similar to that previously noted in this species following surgical castration, any relevance to man has not been established.

4.5. Interaction with other medicines and other forms of interaction

None known.

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 (see section 4.3). 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 (see section 4.4 re: 'time to return of menses').

Breastfeeding:

The use of ZOLADEX 10,8 mg during breastfeeding is contraindicated (see section 4.3).

4.7. Effects on ability to drive and use machines

There is no evidence that ZOLADEX results in impairment of these activities.

4.8. Undesirable effects

The frequencies of adverse events are ranked according to the following:

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (< 1/10 000).

System Organ Class	**Frequency Classification**	**Adverse Reaction**	
		Female	**Male**
Neoplasms benign, malignant and unspecified	Common	Increase in signs and symptoms in breast cancer	
Immune system disorders	Rare	Hypersensitivity reactions[1]	Hypersensitivity reactions[1]
Endocrine disorders	Rare		Pituitary apoplexy[2]
Metabolism and nutrition disorders	Uncommon	Hypercalcaemia (on initiation of therapy)	
Psychiatric disorders	Very common	Change in libido[3], depression	Decrease in potency[4], sexual dysfunction
Nervous system disorders	Very common	Headaches	Non-specific paraesthesias
	Uncommon		Spinal cord compression
Vascular disorders	Very common	Hot flushes[3], transient increases in systolic and diastolic blood pressure levels[5]	Hot flushes[4]
Skin and subcutaneous tissue disorders	Very common	Sweating[3]	Sweating[4]
	Common		Skin rashes[6]

System Organ Class	Frequency Classification	Adverse Reaction	
		Female	**Male**
Musculoskeletal and connective tissue disorders	Common		Reduction in bone mineral density[7], increase in bone pain[7]
	Uncommon		Arthralgia
Renal and urinary disorders	Uncommon		Ureteric obstruction[8]
Reproductive system and breast disorders	Very common	Change in breast size, vaginal dryness	
	Common		Breast swelling
	Uncommon		Breast tenderness
	Rare	Ovarian cyst formation, ovarian hyperstimulation	

1. Hypersensitivity reactions, which may include anaphylaxis, angioedema, urticaria, eczema and bronchospasm.
2. Less frequently cases of pituitary apoplexy have been reported following initial administration of ZOLADEX 3,6 mg.
3. Which may require withdrawal of therapy.
4. Seldom requiring withdrawal of therapy.
5. Changes in blood pressure, 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. In hypertensive patients, blood pressure should be monitored more frequently and therapy may have to be adjusted.

6. Skin rashes have been reported which are generally mild, often regressing without discontinuation of therapy.
7. The use of ZOLADEX may cause a reduction in bone mineral density (see "*Warnings and Special Precautions*"). Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.
8. Following administration of ZOLADEX 10,8 mg isolated cases of ureteric obstruction have been recorded.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists such as ZOLADEX. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus.

Blood lipids (total cholesterol, low density cholesterol, triglycerides) may increase.

Occasional local reactions including mild bruising at the subcutaneous injection sites, have been reported.

The following occasional serious adverse effects have been associated with the use of ZOLADEX: Interstitial lung infiltrates, joint swelling and effusions in joints, carpal tunnel syndrome, and erythema multiforme.

In women with fibroids, degeneration of fibroids may occur resulting in abdomino-pelvic pain, low grade fever, continual bleeding and occasional enlargement of the fibroid and ascites. Pelvic pain, sometimes severe and related to haemorrhage into uterine fibromyoma may occur. Patients should be warned to contact their doctor. Dyspareunia, dysmenorrhoea as well as menorrhagia, uterine and vaginal bleeding have been observed in patients treated for uterine fibroids.

During early ZOLADEX treatment, some women may experience vaginal bleeding of variable duration and intensity. Such bleeding usually represents oestrogen withdrawal bleeding and is expected to stop spontaneously but may also be caused by degenerating fibromyoma. Spotting is common.

During treatment with ZOLADEX, patients may enter the natural menopause. Some women do not resume menses on cessation of therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

There is no human experience of overdosage. 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 10,8 mg.

If overdosage occurs, this should be managed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropin releasing hormone analogues, ATC code: L02AE03.

Goserelin is a synthetic analogue of naturally occurring luteinizing hormone releasing hormone (LHRH), a decapeptide found in the hypothalamus. LHRH controls the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. On chronic

administration goserelin results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum oestradiol concentrations in females. Initially, goserelin transiently increases serum testosterone concentrations in men and serum oestradiol concentrations in women.

In men by around 21 days after the first depot injection of 10,8 mg, testosterone concentrations have fallen to within the castrate range and remain suppressed with treatment every 3 months.

5.2. Pharmacokinetic properties

Administration of 10,8 mg goserelin in accordance with the dosage recommendations ensures that exposure to goserelin is maintained with no clinically significant accumulation.

Goserelin is poorly protein bound and has a serum elimination half-life of 2-4 hours in subjects with normal renal function. The half-life is increased in patients with impaired renal function. For 10,8 mg goserelin given as recommended, 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

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 the 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 and glacial acetic acid.

6.2. Incompatibilities

None known

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in the sealed package at or below 25 °C.

6.5. Nature and contents of container

The injections are supplied as a pre-loaded single-dose disposable syringe applicator.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

8. REGISTRATION NUMBER(S)

30/21.10/0100

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 January 1997

10. DATE OF REVISION OF THE TEXT

02 August 2022

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