

PRODUCT MONOGRAPH

 **ZOLADEX[®]**

Goserelin Depot

3.6 mg Goserelin/depot
(as goserelin acetate)

Luteinizing Hormone - Releasing Hormone Analog
(LHRH Analog)

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PrZOLADEX[®]

Goserelin Depot

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Depot/3.6 mg goserelin	Lactide-glycolide copolymer <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ZOLADEX[®] (goserelin acetate) is indicated for a number of hormone-dependent conditions as shown below under the headings Prostate Cancer, Breast Cancer and Benign Conditions:

Prostate Cancer

- ZOLADEX is indicated for the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate (Stage M1 according to the Tumour-Node-Metastasis [TNM] classification system or Stage D2 according to the American Urologic Association [AUA] classification).
- ZOLADEX is indicated for use in combination with a non-steroidal antiandrogen and radiation therapy for the management of locally advanced (T3, T4) or bulky Stage T2b, T2c carcinoma of the prostate. Treatment with ZOLADEX and a non-steroidal antiandrogen should start 8 weeks prior to initiating radiation therapy and continue until completion of the radiation therapy.
- ZOLADEX as adjuvant hormone therapy to external beam irradiation for patients with locally advanced prostate cancer (Stage T3-T4).

Breast Cancer

- ZOLADEX is indicated as an alternative to standard adjuvant chemotherapy in pre- and perimenopausal women with early breast cancer who are unsuitable for, intolerant to, or decline chemotherapy, and whose tumour contains estrogen and/or progesterone receptors.
- ZOLADEX is indicated for the palliative treatment of advanced breast cancer in pre- and perimenopausal women whose tumour contains estrogen and/or progesterone receptors.

Benign Conditions

- ZOLADEX is indicated for the hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with ZOLADEX for the management of endometriosis has been limited to women 18 years of age and older, treated for 6 months.
- ZOLADEX is indicated for use as an endometrial thinning agent prior to endometrial ablation.

Pediatrics:

The safety and effectiveness of ZOLADEX in children has not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Women having undiagnosed abnormal vaginal bleeding.

Pregnancy:

ZOLADEX should not be used during pregnancy. As with other LHRH agonists it is not known whether ZOLADEX causes fetal abnormalities in humans. Women of child bearing potential should be carefully examined before treatment to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy (see WARNINGS AND PRECAUTIONS).

Lactation:

The use of ZOLADEX during breast feeding is not recommended.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZOLADEX (goserelin acetate) should be prescribed by a qualified physician experienced in the use of hormonal therapy in cancer and endometriosis.

ZOLADEX should be administered by a healthcare professional experienced in administering deep subcutaneous injections and under the supervision of a physician.

The following are clinically significant adverse events:

- Tumour flare reaction (see Tumour Flare Reaction, below)
- Osteoporosis (see Musculoskeletal, below)
- Injection site injuries and vascular injuries (see General, below)

General

Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with ZOLADEX. Monitor patients for signs or symptoms of abdominal hemorrhage. As ZOLADEX requires administration by deep subcutaneous injection, it is not recommended in patients with low body mass index (BMI <18.5) or in patients who are fully anticoagulated (INR >2) due to the risk of vascular injury and subsequent bleeding during administration (see DOSAGE AND ADMINISTRATION).

Initially, ZOLADEX transiently increases serum testosterone in males and serum estradiol concentrations in females and other gonadal hormones. Although not necessarily related, isolated cases of short-term worsening of signs and symptoms have been reported during the first four weeks of therapy. Worsening of the clinical condition may occasionally require discontinuation of therapy and/or surgical intervention.

Effect on ability to drive a vehicle and use machinery: There is no evidence that ZOLADEX results in impairment of ability to drive or operate machinery.

Tumour Flare Reaction

Patients with genitourinary tract symptoms: During the first month of therapy with ZOLADEX, patients at risk of developing ureteric obstruction should be closely

monitored. Ureteric obstruction may develop in male patients with a history of obstructive uropathy.

Patients with vertebral metastases: During the first month of therapy with ZOLADEX, patients with vertebral metastases who are thought to be at particular risk of spinal cord compression should be closely monitored.

If spinal cord compression or renal impairment due to ureteric obstruction are present, or develop, treatment of these complications should be instituted according to current local clinical practice.

Cardiovascular

Androgen deprivation therapy may increase cardiovascular risk in men with prostate cancer on the basis of its adverse impact on demonstrated cardiovascular risk factors, by increasing body weight, reducing insulin sensitivity, and/or resulting in dyslipidemia. Heart failure was commonly reported in patients receiving ZOLADEX for prostate cancer treatment in clinical studies (see ADVERSE REACTIONS/Adverse Drug Reaction Overview). Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered.

Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk, including the potential for torsades de pointes, in patients with a history of QT prolongation, with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications (see DRUG INTERACTIONS). In patients at risk of developing QT/QTc interval prolongation, periodic monitoring of ECG and serum electrolyte levels should be considered (see Monitoring and Laboratory Tests).

In a randomized, active-controlled trial comparing goserelin plus a nonsteroidal antiandrogen to a LHRH antagonist in 177 patients with prostate cancer, periodic electrocardiograms were performed and prospectively evaluated. A mean QTcF increase of 18 msec from baseline was reported for the combination cohort. A total of 8% patients experienced QTcF change \geq 60 msec from baseline and 3 patients were withdrawn for a QT prolongation to $>$ 500 msec in the combination cohort.

Dependence/Tolerance

There have been no reports of drug dependence following the use of ZOLADEX.

Endocrine and Metabolism

Males

Induced hypogonadism: Suppression of pituitary gonadotropins and gonadal hormone production will occur with continued administration of ZOLADEX. These changes have been

observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Metabolic: Impaired glucose tolerance has been observed in males using 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.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

Immune

Antibody formation has not been observed during administration of ZOLADEX. Local reactions, such as mild bruising have been related to the trauma of the injection itself and not to the copolymer material of the depot or to the prolonged presence of ZOLADEX at the site of depot injection.

Musculoskeletal

Changes in bone density: The use of LHRH agonists may cause a reduction in bone mineral density. In men and women, some bone loss can be anticipated as part of the natural aging process. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

Data from studies of ZOLADEX suggest that some recovery of bone mineral may occur on cessation of therapy.

In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as corticosteroids or anticonvulsants, ZOLADEX may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with ZOLADEX is initiated. In women being treated for endometriosis, the use of ZOLADEX for longer than the recommended six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Worsening of bone pain and other signs and symptoms have been reported infrequently in males and to a lesser extent in females during the first month of therapy with ZOLADEX (goserelin acetate). In men, by around 21 days after the first depot injection, testosterone concentrations have typically decreased to within the castrate range and remain suppressed with treatment every 28 days. It is unclear whether there is any relationship between these clinical events and the initial rise in serum testosterone or estradiol levels observed during the first few days following administration of the first depot injection.

In those who reported an increase in bone pain, the pain ranged in intensity from mild to severe and required either symptomatic management, including non-narcotic analgesics or in some severe cases, narcotic analgesics.

Psychiatric

Depression (sometimes severe) has been reported in patients treated with ZOLADEX in post-market surveillance. Patients should be informed of the risks, monitored and treated accordingly (see ADVERSE REACTIONS).

Sexual Function/Reproduction

Fertility: Suppression of serum estradiol will induce amenorrhea in the majority of patients after the first four weeks of treatment especially if started during the menstrual phase of the cycle. During early treatment with ZOLADEX some women may experience vaginal bleeding of variable duration and intensity. Such bleeding may represent estrogen withdrawal bleeding and is expected to stop spontaneously. Amenorrhea is expected to be maintained until 4 weeks after the last dose of ZOLADEX.

Menses usually resumed within 8 weeks following completion of therapy. Rarely, some women may enter the natural menopause during treatment with LHRH analogues and do not resume menses on cessation of therapy.

Time to return of menses after cessation of therapy with ZOLADEX may be prolonged in some patients.

A non-hormonal method of contraception should be used during treatment. Patients should be advised that if they miss or postpone a dose of ZOLADEX, ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

Duration of endometriosis treatment: The safety of treatment, as well as re-treatment, beyond 6 months with ZOLADEX has not been established.

Endometrial thinning: The use of ZOLADEX may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix.

Special Populations

Pregnant Women: ZOLADEX should not be used in pregnancy as there is a theoretical risk of abortion or fetal 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 until menses resume.

Nursing Women: The use of ZOLADEX during breast feeding is not recommended.

Pediatrics: The safety and effectiveness of ZOLADEX in children has not been established.

Geriatrics: The labelling reflects the safety and effectiveness of ZOLADEX in the population over 65 years of age.

Monitoring and Laboratory Tests

Monitoring of patients

During therapy with ZOLADEX, patients should be routinely monitored by physical examinations and appropriate laboratory tests. In prostate cancer patients tumour markers such as prostatic acid phosphatase (PAP), prostatic specific antigen (PSA) or acid phosphatase could be monitored. Additionally, if deemed appropriate by the physician, serum testosterone or serum estradiol may be monitored; however, this is not routinely required.

In prostate cancer patients, an assessment of bone lesions may require the use of bone scans. Prostatic lesions may be monitored by ultrasonography and/or CT scan in addition to digital rectal examination. The status of obstructive uropathy in males may be assessed and/or diagnosed using intravenous pyelography, ultrasonography or CT scan.

Impaired glucose tolerance has been observed in males using 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.

Baseline measurements of ECG, serum potassium, calcium, and magnesium levels should be considered. Monitoring of ECG and serum electrolyte levels during treatment should also be considered in patients at risk.

Effect on Laboratory Tests

Although serum testosterone or serum estradiol may be elevated during the first few days after administration of the first depot, they return to normal within one week, and are suppressed by the end of three weeks. They remain suppressed throughout therapy with ZOLADEX.

Prostate cancer tumour markers (PSA and PAP), are not routinely monitored in the first few days of therapy; however, if the cancer is responsive to ZOLADEX therapy, then these levels, if elevated prior to the commencement of treatment, are usually reduced by the end of the first month.

Renal function tests, blood urea nitrogen and creatinine may rarely be elevated during the first few days of therapy in prostate cancer patients before returning to normal.

Diagnostic interference

Administration of ZOLADEX in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored approximately 8 weeks after the last dose of ZOLADEX. Diagnostic tests of pituitary-gonadal function conducted during the treatment and within 8 weeks after discontinuation of ZOLADEX therapy may therefore be misleading.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse effects seen with ZOLADEX (goserelin acetate) are due primarily to its pharmacologic action of sex hormone suppression and may give rise to certain expected effects that vary by sex.

Adverse events that have been observed at an equal frequency in both males and females follow. Very common adverse events ($\geq 10\%$) consist of: decreased libido, hot flush, and hyperhidrosis. These are pharmacological effects which seldom require withdrawal of therapy. Common adverse reactions ($\geq 1\%$ to $<10\%$) are: paraesthesia, abnormal blood pressure, rash, weight increase, and decrease in bone density. Drug hypersensitivity was reported uncommonly ($\geq 0.1\%$ to $<1\%$). Anaphylactic reaction has been reported rarely ($\geq 0.01\%$ to $<0.1\%$). Cases of pituitary tumours and psychotic disorder have also been occasionally reported during post-marketed use. As with other agents in this class, cases of pituitary hemorrhage have occasionally been reported following initial administration of ZOLADEX during post-marketed use.

Abnormal blood pressure, manifest as hypotension or hypertension are commonly observed in patients administered ZOLADEX. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with ZOLADEX. Such changes have rarely required medical intervention including withdrawal of ZOLADEX treatment.

In males, erectile dysfunction was reported very commonly ($\geq 10\%$). Commonly reported adverse reactions ($\geq 1\%$ to $<10\%$) consist of: impaired glucose tolerance, spinal cord compression, bone pain, gynecomastia, mood swings, depression, cardiac failure and injection site reaction. Uncommon adverse reactions ($\geq 0.1\%$ to $<1\%$) are: arthralgia, ureteric obstruction and breast tenderness.

Alopecia, particularly the loss of body hair, is an expected effect of lowered androgen levels and has been reported in males at an unknown frequency.

Heart failure was commonly reported (5%) in patients receiving ZOLADEX for prostate cancer treatment in clinical studies. Serious myocardial infarction and heart failure were observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risks for these cardiovascular adverse events appear to be increased when LHRH agonists are used in combination with anti-androgens.

In females, very common adverse reactions ($\geq 10\%$) consist of: vulvovaginal dryness, breast enlargement, injection site reaction and acne (in most cases, acne was reported within one month after the start of ZOLADEX). Common adverse reactions ($\geq 1\%$ to $<10\%$) are: mood alteration including depression, headache, arthralgia and tumour flare/tumor pain. Hypercalcemia occurs at an uncommon frequency ($\geq 0.1\%$ to $<1\%$). Rare ($\geq 0.01\%$ to $<0.1\%$) cases of ovarian cyst have been reported. At the beginning of ZOLADEX treatment,

abdominal pain, bleeding, loss of necrotic tissue and abdominal distension have been reported in patients with uterine fibroid at an unknown frequency.

Loss of head hair (alopecia) has been reported commonly in females, including in younger patients treated for benign conditions. This is usually mild but occasionally can be severe.

Following the administration of ZOLADEX, skin rashes have been reported as generally mild, often regressing without discontinuation of therapy.

Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.

The use of LHRH agonists may cause a reduction in bone mineral density (see WARNINGS AND PRECAUTIONS).

Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported in clinical trials (6/10 874; 0.06%) and post-market use of ZOLADEX.

Clinical Trial Adverse Drug Reactions

Prostate Cancer Patients

Five hundred and eighteen (518) patients with prostate cancer who had not been previously treated and who entered into 14 open multicentre studies were monitored for adverse reactions to ZOLADEX. The mean duration of treatment in these patients was 23 weeks.

The following reports from these clinical trials are considered to be possibly related to treatment with ZOLADEX: hot flush (51%), decreased libido (53%), decreased erections (57%), breast tenderness (3%), gynecomastia (2%), local intolerance at injection site (pain, erythema) (4%), and skin rash including erythema and urticaria (1.9%).

Also in these clinical studies, an initial rise in mean serum testosterone levels occurred during the first few days of treatment with ZOLADEX. In a few instances, patients experienced a worsening of signs and symptoms, during the first month after initiation of therapy (see WARNINGS AND PRECAUTIONS). For these patients, this was usually an increase in bone pain (4.2%), however, isolated cases of ureteric obstruction (1.1%) and/or spinal cord compression (1.2%) have also been reported during the initial four weeks of ZOLADEX therapy. The relationship of these observations to ZOLADEX is unknown.

The potential for exacerbation of signs and symptoms during the first few weeks of treatment is a concern particularly in male patients with impending neurologic compromise and in patients with severe obstructive uropathy (see WARNINGS AND PRECAUTIONS).

The most frequently reported (greater than 5%) adverse experiences during treatment with a LHRH-agonist in combination with flutamide are listed in the table below. For comparison, adverse experiences seen with a LHRH-agonist and placebo are also listed in the following table.

Table 1 Adverse events (greater than 5%) reported during treatment with a LHRH-agonist in combination with flutamide

	(n=294) Flutamide + LHRH-agonist % All	(n=285) Placebo + LHRH-agonist % All
Hot Flush	61	57
Loss of Libido	36	31
Impotence	33	29
Diarrhea	12	4
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other GI	6	4

As shown Table 1, for both treatment groups, the most frequently occurring adverse experiences (hot flush, loss of libido, impotence) were those known to be associated with low serum androgen levels and known to occur with LHRH-agonists alone.

The only notable difference between these treatment groups was the higher incidence of diarrhea in the flutamide+LHRH-agonist group (12%) as compared to the placebo+LHRH-agonist group (4%). The cases of diarrhea reported were severe in less than 1% of the patients. In addition, the following adverse reactions were reported during treatment with flutamide+LHRH-agonist. No causal relatedness of these reactions to drug treatment has been made, and some of the adverse experiences reported are those that commonly occur in elderly patients.

Cardiovascular System: Hypertension in 1% of patients. Rarely, thrombophlebitis, pulmonary embolism, and myocardial infarction.

Central Nervous System: CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients. Rarely insomnia, tiredness, headache, dizziness, weakness, malaise, blurred vision and decreased libido have been reported.

Endocrine System: Gynecomastia in 9% of patients. Rarely breast tenderness sometimes accompanied by galactorrhoea.

Gastrointestinal System: Nausea/vomiting occurred in 11%; diarrhea 12%, anorexia 4%, and other GI disorders occurred in 6% of patients. Increased appetite, indigestion and constipation have also been reported.

Hematopoietic System: Anaemia occurred in 6% of patients, leukopenia 3%, and thrombocytopenia 1%.

Liver and Biliary System: Clinically evident hepatitis and jaundice occurred in <1% of patients.

Skin: Irritation at the injection site and rash occurred in 3% of patients. Photosensitivity reactions have been reported in five patients.

Other: Pruritus, ecchymosis, herpes zoster, thirst, lymphedema, lupus-like syndrome, hematuria, reduced sperm counts have been reported rarely in long-term treatment. Edema occurred in 4% of patients; neuromuscular, genitourinary symptoms occurred in 2% of patients. Pulmonary symptoms occurred in <1% of patients.

Advanced Breast Cancer Patients

The adverse event profile for women with advanced breast cancer treated with ZOLADEX is consistent with the profile described for women treated with ZOLADEX for endometriosis. In very rare instances, breast cancer patients with bony metastases have developed hypercalcemia on initiation of therapy. In a controlled clinical trial (SWOG-8692) comparing ZOLADEX with oophorectomy in premenopausal and perimenopausal women with advanced breast cancer, the following events were reported at a frequency of 5% or greater in either treatment group regardless of causality.

Table 2 Adverse Reactions– Advanced Breast Cancer Patients

Adverse Reactions	Advanced Breast Cancer Patients	
	ZOLADEX n=57 %	Oophorectomy n=55 %
Hot flush	70	47
Tumour Flare	23	4
Nausea	11	7
Edema	5	0
Malaise/fatigue/lethargy	5	2
Vomiting	4	7

In the Phase II clinical trial program in 333 pre- and perimenopausal women with advanced breast cancer, hot flush and decreased libido were assessed by specific patient inquiry. Hot flush occurred in 75.9 % of the 203 women in whom they were not present at baseline and decreased libido occurred in 47.7% of the 194 women with libido present at baseline. These events reflect the pharmacological actions of ZOLADEX.

Injection site reaction was reported in less than 1% of patients.

Early Breast Cancer Patients

The most frequently recorded possible adverse drug reactions, regardless of causality, for pre- and perimenopausal women aged ≤ 50 years with early breast cancer who received ZOLADEX (N=803) in an open randomized trial (ZEBRA) were headache (5.5%), pain (3.4%) and bone pain (3.4%).

Patients in the study who received ZOLADEX experienced higher incidences of the effects caused by estradiol suppression, e.g. hot flush, vulvovaginal dryness/soreness, and loss of libido, than those experienced in the cyclophosphamide, methotrexate and 5-fluorouracil (CMF) comparator treatment group. Within 6 months of completing ZOLADEX therapy, these incidences had decreased to below those seen in the CMF patients.

The table below lists the frequencies $\geq 1\%$ of adverse drug reactions considered 'extremely likely' or 'probably' related to trial therapy (ZEBRA Trial, median follow-up of 7.5 years).

Table 3 Frequencies $\geq 1\%$ of Adverse Drug Reactions (By COSTART Term) Considered 'Extremely Likely' or 'Probably' Related to Trial Therapy

Body system and COSTART term ^{a,b}	Number (%) of patients	
	ZOLADEX (N=803)	CMF (N=802)
Whole Body		
Headache	24 (3.0)	7 (0.9)
Pain	9 (1.1)	2 (0.2)
Asthenia	5 (0.6)	8 (1.0)
Cardiovascular		
Hypertension	14 (1.7)	1 (0.1)
Digestive		
Vomiting	4 (0.5)	84 (10.5)
Nausea	3 (0.4)	62 (7.7)
Hemic and Lymphatic		
Leukopenia	0 (0.0)	70 (8.7)
Metabolic and nutritional		
Weight gain	13 (1.6)	13 (1.6)
ALT increased	1 (0.1)	9 (1.1)
Musculoskeletal		
Bone pain	17 (2.1)	3 (0.4)

Body system and COSTART term ^{a,b}	Number (%) of patients	
	ZOLADEX (N=803)	CMF (N=802)
Osteoporosis	11 (1.4)	4 (0.5)
Skin and appendages		
Rash	4 (0.5)	8 (1.0)
Special senses		
Conjunctivitis	1 (0.1)	9 (1.1)
Urogenital		
Metrorrhagia	10 (1.2)	1 (0.1)

^a A patient may have had more than one adverse event that was considered "extremely likely" or "probably" related to trial therapy.

^b Thirteen (1.6%) patients who received ZOLADEX, and 0 (0.0%) patients, who received CMF, recorded possible adverse reactions considered "extremely likely" or "probably" related to trial therapy that could not be attributed to a COSTART term.

ALT: Alanine aminotransferase (SGPT)

COSTART: Coding Symbols for Thesaurus of Adverse Reaction Terms.

Benign Conditions

In controlled clinical trials, comparing ZOLADEX every 28 days with danazol daily for the treatment of endometriosis, the following events elicited by direct questioning were reported at a frequency of 5% or more.

Table 4 Adverse Reactions Reported in Endometriosis Trials

ADVERSE REACTIONS	Endometriosis Trials	
	ZOLADEX treated n=411 %	Danazol treated n=207 %
Hot Flush	96	67
Vaginitis (Vulvovaginal Dryness)	75	43
Headache	75	63
Emotional Lability (Mood swings)	60	56
Libido Decreased	61	44
Hyperhidrosis	45	30
Depression	54	48
Acne	42	55
Breast Atrophy	33	42
Seborrhea	26	52

ADVERSE REACTIONS	Endometriosis Trials	
	ZOLADEX treated n=411 %	Danazol treated n=207 %
Peripheral Edema	21	34
Breast Enlargement	18	15
Pelvic Symptoms	18	23
Pain	17	16
Dyspareunia	14	5
Libido Increased	12	19
Infection	13	11
Asthenia	11	13
Nausea	8	14
Hirsutism	7	15
Insomnia	11	4
Breast Pain	7	4
Abdominal Pain	7	7
Back Pain	7	13
Flu Syndrome	5	5
Dizziness	6	4
Application Site Reaction	6	
Voice Alterations	3	8
Pharyngitis	5	2
Hair Disorders	4	11
Myalgia	3	11
Nervousness	3	5
Weight Gain	3	23
Leg Cramps	2	6
Increased Appetite	2	5
Pruritis	2	6
Hypertonia	1	10

From the endometriosis trials and other supporting safety studies, other adverse reactions, not listed above, elicited at a frequency of 1% or more are shown below. The relationship of these possible adverse reactions to therapy with ZOLADEX is unknown.

Whole body: allergic reaction, chest pain, fever, malaise

Cardiovascular: hemorrhage, hypertension, migraine, palpitations, tachycardia

Digestive: anorexia, constipation, diarrhea, dry mouth, dyspepsia, flatulence

Hemic and lymphatic: ecchymosis

Metabolic and nutritional: edema

Musculoskeletal: arthralgia, joint disorder

Nervous: anxiety, paresthesia, somnolence, thinking abnormal

Respiratory: bronchitis, cough increased, epistaxis, pharyngitis, rhinitis, sinusitis

Skin: alopecia, dry skin, rash, pruritus, skin discoloration

Special senses: amblyopia, dry eyes

Urogenital: dysmenorrhea, urinary frequency, urinary tract infection, vaginal hemorrhage

As with other LHRH agonists, there have been reports of ovarian cyst formation.

Changes in Bone Mineral Density

After 6 months of ZOLADEX treatment, 97 female patients treated with ZOLADEX for endometriosis showed an average 4.6% decrease of vertebral trabecular bone mineral density (BMD) as compared to pretreatment values. BMD was measured by dual-photon absorptiometry or dual energy x-ray absorptiometry. Forty-four of these patients were assessed for BMD loss 6 months after the completion (post-therapy) of the 6-month therapy period. Data from these patients showed an average 2.6% BMD loss compared to pretreatment values. Nine of the 97 patients were assessed for BMD at 12 months post-therapy. Data from these patients showed an average decrease of 2.5% in BMD compared to pretreatment values. These data suggest a possibility of partial reversibility.

In the ZEBRA study, a subgroup of patients were investigated for possible changes to bone mineral during their breast cancer treatment which consisted of 6 cycles of CMF or 2 years of ZOLADEX. The percentage change from baseline in BMD was assessed at 1, 2 and 3 years for both the lumbar spine and the femoral neck. Figures 1 and 2 show that patients in both treatment groups lose bone mineral and continue to do so between 1 and 2 years following the start of treatment. However, by 3 years, one year after the end of ZOLADEX treatment, patients in the ZOLADEX group show partial recovery of bone mineral. The percentage

change from baseline at both the lumbar spine and femoral neck at 3 years was less in the ZOLADEX than in the CMF group.

Figure 1 Percentage Change From Baseline In BMD (means ± SEM) - Lumbar Spine. Numbers Of Patients Are Shown In Parentheses.

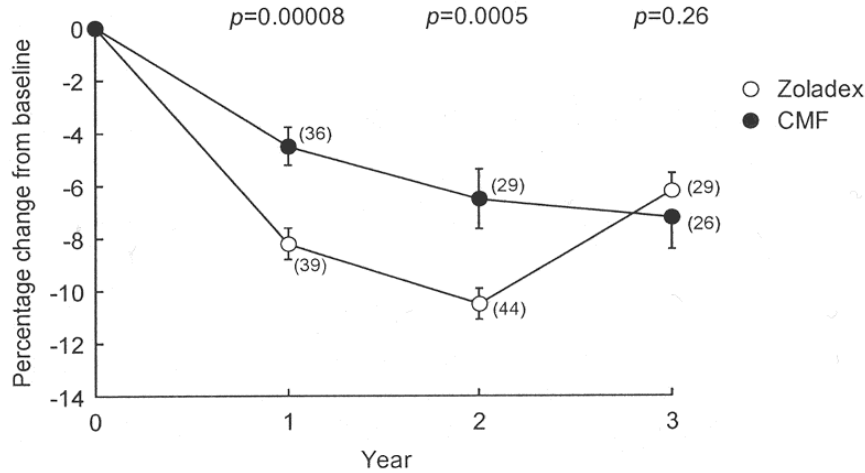
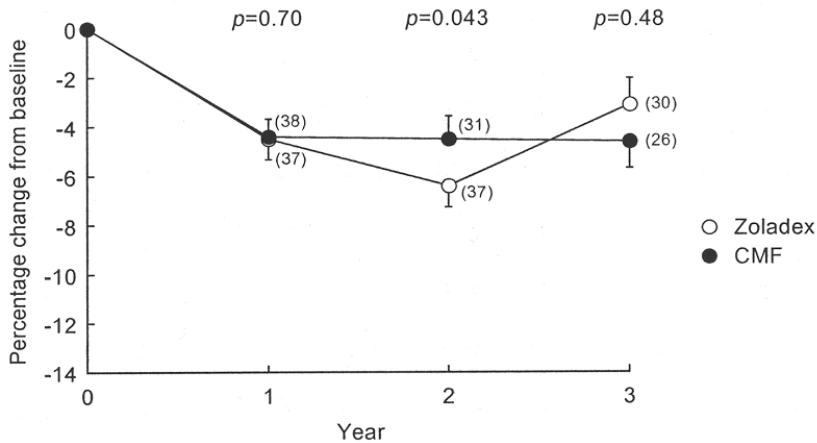


Figure 2 Percentage Change From Baseline In BMD (means ± SEM) - Neck Of Femur. Numbers Of Patients Are Shown In Parentheses



Less Common Clinical Trial Adverse Drug Reactions (<1%)

When 942 male patients treated with ZOLADEX are considered, the adverse reactions listed below were reported to occur in less than 1% of patients with the exception of bone pain (2.9%), increased alkaline phosphatase (2.4%) and nausea/vomiting (1.4%).

Possible adverse reactions reported in the 942 male patients were as follows:

Cardiovascular: Thrombophlebitis, pulmonary embolism, edema, tachycardia, atrial fibrillation, angina pectoris, congestive cardiac failure, hypertension, myocardial infarction, deep vein thrombosis, palpitations, cerebrovascular accident, central retinal vein thrombosis.

Dermatologic: Pruritus, skin rashes including erythema, eczema and urticaria, worsening of ecchymoses and hair growth.

Gastrointestinal: Dry mouth/thirst, polydipsia, nausea, vomiting, hematemesis, diarrhea, pain in abdomen, constipation, anorexia, flatulence, intolerance to alcohol, gingival atrophy.

Hematologic/Lymphatic: Neutropenia, neutrophilia, lymphocytopenia, lymphocytosis, lowered protein/albumin and palpable lymph nodes.

Musculoskeletal: Bone pain, signs and symptoms of spinal cord compression, (eg., paresthesia, paraparesis, paraplegia), muscular fatigue, myopathy, pain (other than bone), hyperesthesia, arthritis, suprapubic pain, polyarthralgia and neurological troubles with lower limbs.

Central Nervous System: Vertigo, headaches, blackouts, flashes of light, decreased/blurred vision, glaucoma, drowsiness, lassitude, lethargy, malaise, disorientation, mental confusion, sensitivity to noise, taste disturbance.

Urogenital: Renal impairment, renal tract obstruction, urinary retention, chronic renal failure, hydronephrosis, nocturia, testicular atrophy.

Laboratory Values: Elevation of liver function test parameters, (eg., gamma GT, alanine aminotransferase, aspartate aminotransferase, and bilirubin), raised alkaline phosphatase, serum calcium and hyperkalemia.

Miscellaneous: Fever, sore throat, influenza, herpes zoster, gangrene, decreased appetite.

Abnormal Hematologic and Clinical Chemistry Findings

Plasma enzymes

Elevations of liver enzymes (AST, ALT) have been reported in less than 1% of all female patients. There was no other evidence of abnormal liver function. Causality between these changes and ZOLADEX have not been established.

Lipids

In a controlled trial, ZOLADEX therapy resulted in a minor, but statistically significant effect on serum lipids. In patients treated for endometriosis at 6 months following initiation of therapy, ZOLADEX treatment resulted in mean increases in LDL cholesterol of 0.55 mmol/L and HDL cholesterol of 0.07 mmol/L. Triglycerides increased by 0.09 mmol/L as well as total cholesterol by 0.65 mmol/L. At the end of 6 months of treatment, HDL cholesterol fractions (HDL2 and HDL3) were increased by 0.05 mmol/L and 0.02 mmol/L, respectively.

In the pivotal trials for endometrial thinning (n=258), the adverse reaction profile for ZOLADEX was similar to that seen in the endometriosis trials, however the frequency was generally lower.

DRUG INTERACTIONS

Drug-Drug Interactions

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of ZOLADEX with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated (see WARNINGS AND PRECAUTIONS, Cardiovascular). Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), pentamidine, antimalarials (e.g. quinine), azole antifungals, cisapride, 5-hydroxytryptamine (5-HT₃) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

Drug-Food Interactions

Interactions with particular foods have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General

ZOLADEX should be administered by a healthcare professional experienced in administering deep subcutaneous injections and under the supervision of a physician (see Serious Warnings and Precautions).

Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with ZOLADEX. As ZOLADEX requires administration by deep subcutaneous injection, caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

As ZOLADEX requires administration by deep subcutaneous injection, it is not recommended in patients with low body mass index (BMI <18.5) or in patients who are fully anticoagulated (INR >2) due to the risk of vascular injury and subsequent bleeding during administration (see WARNINGS AND PRECAUTIONS, General).

Although, isolated cases of vaginal spotting or bleeding during treatment have been reported, this is not associated with lack of pharmacodynamic effect in most instances. The majority of patients become amenorrheic within 8 weeks of starting treatment. In the small number of women who experience continued menstrual bleeding, estradiol blood levels should be measured. If menstrual bleeding persists and estradiol measurements correspond to postmenopausal values, appropriate diagnostic measures should be undertaken to rule out an intrauterine pathology.

Recommended Dose and Dosage Adjustment

Breast Cancer

ZOLADEX depot, containing goserelin acetate equivalent to 3.6 mg goserelin, should be administered subcutaneously every 28 days into the anterior abdominal wall following the procedure recommended in the administration instructions (see-Directions for Use attached to sterile pouch).

Available data to date demonstrates that two years of adjuvant ZOLADEX therapy, 3.6 mg every 28 days, has been found to be at least equivalent to standard CMF regimens in terms of overall survival and equivalent to CMF in terms of disease-free survival in pre- and perimenopausal patients with early breast cancer and whose tumour is estrogen receptor-positive.

Prostate Cancer

When ZOLADEX is given in combination with a non-steroidal antiandrogen and radiotherapy for patients with Stage T2b-T4 prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue until completion of the radiation therapy. A treatment regimen using a ZOLADEX 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the ZOLADEX LA (10.8 mg) depot, can be administered by injection subcutaneously into the anterior abdominal wall.

Alternatively, four injections of the ZOLADEX 3.6 mg depot subcutaneously into the anterior abdominal wall can be administered at 28 day intervals, two depots preceding and two during radiotherapy until completion of the radiation therapy.

Endometriosis

One depot of ZOLADEX containing goserelin acetate equivalent to 3.6 mg goserelin, should be injected subcutaneously into the anterior abdominal wall every 28 days following the procedure recommended in the administration instructions (see-Directions for Use attached to sterile pouch).

Endometrial Thinning

For use as an endometrial thinning agent prior to endometrial ablation, ZOLADEX should be administered by subcutaneous injection into the anterior abdominal wall as two 3.6 mg depots, four weeks apart, with surgery planned for between 0 and 2 weeks after the second depot injection.

Renal Impairment

In clinical studies, subjects with impaired renal function (creatinine clearance <20 mL/min) had a mean serum elimination half-life of 12.1 hours for ZOLADEX compared to 4.2 hours for male subjects with normal renal function (creatinine clearance >70 mL/min). This increase of approximately 8 hours in serum half-life is insufficient to warrant extending the 28-day dosing interval of the 3.6 mg depot, but will lead to modestly higher serum concentrations of the drug in such patients. No dose adjustment, therefore, is necessary for patients with renal failure.

Hepatic Impairment

Hepatic impairment does not compromise the clearance of ZOLADEX, therefore, a dosage adjustment is not needed for patients with hepatic impairment.

Geriatrics

No dosage adjustment is necessary in the elderly.

Pediatrics

The safety and effectiveness of ZOLADEX in children has not been established.

Administration

ZOLADEX is administered by deep subcutaneous injection into the anterior abdominal wall below the navel line. Caution should be taken while injecting ZOLADEX due to the proximity of underlying inferior epigastric artery and its branches. Follow all administration instructions.

Caution: Use only if pouch is undamaged. Use immediately after opening pouch. Do not depress plunger until Step 5. **Read all instructions before use.**

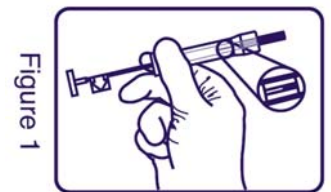
ZOLADEX 3.6 mg Step by Step Directions for Use

ZOLADEX should be administered using an aseptic technique.

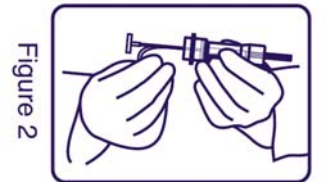
1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare an area of the anterior abdominal wall below the navel line with an alcohol swab.

Note: As ZOLADEX requires administration by deep subcutaneous injection, caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches. The use of ZOLADEX is not recommended in very thin patients (BMI < 18.5) as they may be at higher risk of vascular injury.

2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light. Check that at least part of the ZOLADEX depot is visible (**Figure 1**).

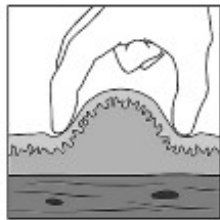


3. Grasp the plastic safety tab and pull away from the syringe and discard (**Figure 2**). Remove needle cover. **Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the depot.**

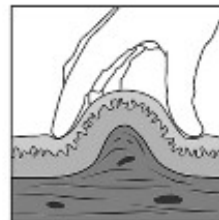


4. Holding the syringe around the protective sleeve, **pinch the skin of the patient's anterior abdominal wall below the navel line.**

Correctly lifted skin fold:



Incorrectly lifted skin fold:



With the opening of the needle facing up, **insert needle at a slight angle (30 to 45 degrees) to the skin into the subcutaneous tissue** of the anterior abdominal wall below the navel line, until the protective sleeve touches the patient's skin (**Figure 3**).



Do not penetrate into muscle or peritoneum. Incorrect grip and angle of administration is shown (**Figure 4**).



Note: The ZOLADEX syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and immediately control any resultant bleeding, monitoring the patient for signs or symptoms of abdominal hemorrhage. After ensuring the patient is hemodynamically stable another ZOLADEX depot may be injected with a new syringe elsewhere. The use of ZOLADEX is not recommended in patients with a low BMI (< 18.5) and/or to patients who are fully anticoagulated (INR > 2).

5. Moving your hand back to the finger grip, depress the plunger **fully**, until you can depress no more, to discharge the ZOLADEX depot and to activate the protective sleeve. You may hear a 'click' and will feel the protective sleeve automatically begin to slide to cover the needle. If the plunger is not depressed fully the protective sleeve will **NOT** activate.

Note: The needle does not retract.

6. Holding the syringe as shown in **Figure 5**, withdraw the needle and allow protective sleeve to continue to slide and cover needle. Dispose of the syringe in an approved sharps collector.



Note: In the unlikely event of the need to surgically remove a ZOLADEX depot, it may be localized by ultrasound.

OVERDOSAGE

The pharmacologic properties of ZOLADEX (goserelin acetate) and its mode of delivery make accidental or intentional overdose unlikely. There is limited experience of overdose in humans. In cases where ZOLADEX has unintentionally been readministered early or given at a higher dose than recommended, no clinically relevant adverse effects have been seen. Animal studies indicate that no increased pharmacologic effect would occur in man with higher doses or more frequent administration than those recommended. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs produced no non-endocrine related sequelae; this dose is approximately 400 times that proposed for human use. If overdose occurs, this should be managed symptomatically.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ZOLADEX (goserelin acetate) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH or LHRH). When given acutely, goserelin acetate releases luteinizing

hormone (LH) from the pituitary gland. However, following chronic administration, goserelin acetate is a potent inhibitor of gonadotropin production resulting in gonadal and consequently, accessory sex organ regression. This effect is the basis for the inhibition of growth of chemically-induced rat mammary tumours and transplantable rat prostate and pituitary tumours.

In animals and man, following an initial stimulation of pituitary LH secretion and a transient elevation in serum testosterone in males and serum estradiol in females, chronic administration results in inhibition of gonadotropin secretion.

Approximately 21 days after the initiation of therapy, a sustained suppression of pituitary LH results for men in the reduction of serum testosterone levels to a range normally seen in surgically castrated men, and for women in the reduction of serum estradiol to levels comparable with those observed in postmenopausal women. This suppression of testosterone and estradiol is then maintained as long as therapy is continued.

When used in women this suppression of serum estradiol is associated with endometrial thinning, suppression of follicular development within the ovary and a response in hormone dependent breast cancer (tumours that are estrogen receptor (ER) - positive and/or progesterone receptor (Pg R) - positive), and endometriosis. Suppression of serum estradiol will induce amenorrhea in the majority of patients after the first four weeks of treatment especially if started during the menstrual phase of the cycle. During early treatment with ZOLADEX some women may experience vaginal bleeding of variable duration and intensity. Such bleeding may represent estrogen withdrawal bleeding and is expected to stop spontaneously. Amenorrhea is expected to be maintained until 4 weeks after the last dose of ZOLADEX.

ZOLADEX is a depot formulation of goserelin acetate dispersed in a cylindrical rod of biodegradable and biocompatible blend of high and low molecular weight range D-L Lactide-glycolide copolymer.

The bioavailability of goserelin acetate from ZOLADEX depot is almost complete. When injected subcutaneously, goserelin is released continuously over at least 28 days.

Administration of a depot every four weeks ensures that effective concentrations are maintained with no accumulation.

ZOLADEX is poorly protein bound and has a serum elimination half-life of about 4.2 hours in male subjects and 2.3 hours in female subjects with normal renal function. Although the half-life is increased in patients with impaired renal function, this has minimal effects, and hence, no change from a monthly dosing schedule is necessary. There is no significant change in the clearance of ZOLADEX in patients with hepatic impairment with normal renal function (see DETAILED PHARMACOLOGY).

Pharmacodynamics

Daily doses of goserelin acetate of 25 to 500 µg in the aqueous formulation induce pituitary desensitization to endogenous and exogenous LHRH and after 7 to 21 days depress serum LH and testosterone. These findings indicate the locus of effect of goserelin acetate in man is at the pituitary gland. Initially, ZOLADEX like other LHRH agonists transiently increases serum testosterone concentrations.

In women, serum estradiol concentrations are suppressed by around 21 days 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. Suppression of estradiol is associated with a response in endometriosis and will result in amenorrhoea in the majority of patients. Administration of goserelin acetate in a depot formulation every 28 days results in suppression of serum testosterone concentrations to that usually seen in the surgically castrate range and suppression of serum estradiol levels comparable to those seen postmenopausally.

Pharmacokinetics

Administration of ZOLADEX, in accordance with the dosage 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 about 4.2 hours in male subjects and 2.3 hours in female subjects with normal renal function. Although the half-life is increased in patients with impaired renal function absolute clearance is still relatively rapid. The existence of a non-renal, presumably hepatic, clearance and the absence of an increased incidence of possible adverse reactions in such patients implies that no adjustment in the proposed dosage regimen is necessary in patients with renal impairment. There is no significant change in the clearance of ZOLADEX in patients with hepatic impairment with normal renal function. The depot formulation of goserelin acetate releases drug continuously with peak serum concentrations occurring approximately two weeks after administration. Comparison of the pharmacokinetic profile of the 3.6 mg depot formulation with that of daily injections of goserelin acetate in the aqueous formulation at doses of 250 µg/day, indicated good bioavailability of the goserelin acetate depot formulation.

There is no evidence of drug accumulation when goserelin acetate depot is administered every 28 days.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of ZOLADEX in children has not been established.

Geriatrics: No dosage adjustment is necessary in the elderly (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: There is no significant change in pharmacokinetics in patients with hepatic failure. Hepatic impairment does not compromise the clearance of ZOLADEX,

therefore a dosage adjustment is not needed for patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: In patients with impaired renal function, the serum half-life is increased (serum half-life is 2-4 hours in patients with normal renal function). When ZOLADEX is given, as recommended, this change will not lead to any accumulation hence, no change in dosing is necessary (see DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Protect from light and moisture. Store in the intact package between 2°C and 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZOLADEX (goserelin acetate) depot is supplied as a cylindrical rod of biodegradable and biocompatible D-L Lactide-glycolide copolymer. Each ZOLADEX depot contains goserelin acetate equivalent to 3.6 mg of goserelin. This depot is presented in a sterile ready-to-use syringe with a 16 gauge needle for a single subcutaneous injection. This single-dose syringe is assembled with a protective sleeve (SafeSystem™) in a sealed, sterile pouch that contains a desiccant. Instructions for administration, once every 28 days, are attached.

Active Constituent: goserelin acetate equivalent to 3.6 mg goserelin per depot.

Other Constituents: Lactide-glycolide copolymer to total weight 18.0 mg per depot.

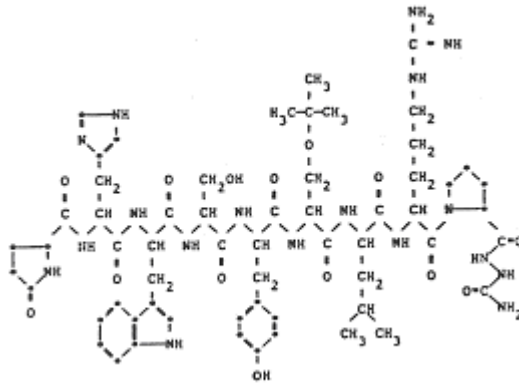
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Goserelin acetate
Chemical Name:	L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D (O- <i>tert</i> -butyl)seryl-L-leucyl-L-arginyl-L-prolyl-azaglycine amide acetate
Abbreviated Chemical Name	L-Glp-L-His-L-Trp-L-Ser-L-Tyr-D-Ser(But)-L-Leu-L-Arg- L-Pro-AzGlyNH ₂ acetate
Other Names	6-D-(O- <i>tert</i> -butyl)serine-10-azaglycine amide- LH-RH, acetate salt
Molecular Formula and Molecular Mass (Free Base):	C ₅₉ H ₈₄ N ₁₈ O ₁₄ 1269.44

Structural Formula:



Physiochemical Properties: Goserelin acetate is a white to off-white powder. It is freely soluble in glacial acetic acid, soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethylsulphoxide. It is practically insoluble in acetone, chloroform and diethyl ether. Measured pK_a (base) is 6.2 (associated with the protonation of the histidine residue). pH of a 2% aqueous solution is approximately 6 (dependent on level of acetic acid present). Oil/Water Coefficient of Partition: Soluble in water, insoluble in n-octanol.

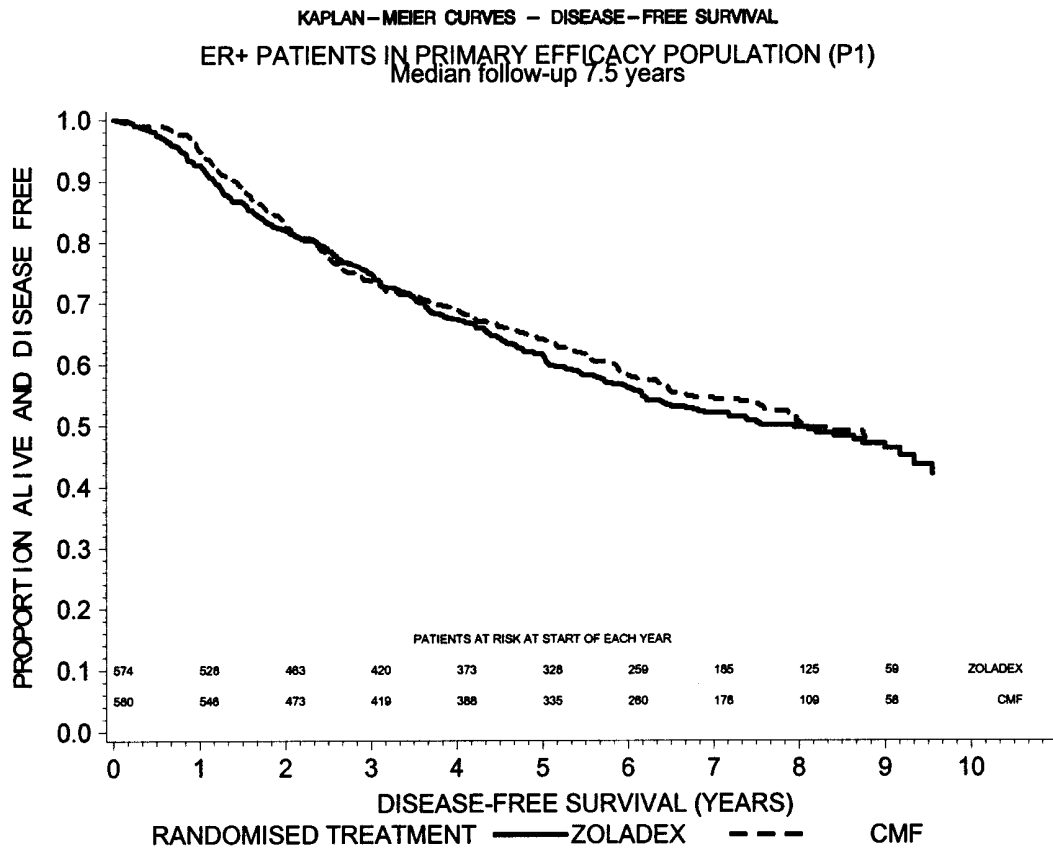
CLINICAL TRIALS

Treatment of Pre- and Perimenopausal Women with Early Breast Cancer - Alternative to Adjuvant Chemotherapy

Pre- and perimenopausal women aged ≤ 50 years with node-positive, stage II breast cancer were randomized to receive adjuvant therapy with either ZOLADEX 3.6 mg 4- weekly for 2 years (817 patients), or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) for six 28-day cycles (823 patients) (ZEBRA Trial). Two administration schedules were employed for patients randomized to the CMF treatment arm: an oral regimen (C: 100 mg/m² po Days 1-14; M: 40 mg/m² IV Days 1 and 8; 5FU: 600 mg/m² IV days 1 and 8; repeated q28 days for 6 cycles) or an IV regimen of CMF containing 500/40/600 mg/m² Days 1 and 8 for 6 cycles. Of the patients randomized to the CMF treatment arm, 17% received the oral regimen and 83% received the IV regimen. The estrogen receptor (ER) status of the primary tumour was established for over 92% of patients in the primary efficacy population, and the percentages of patients with ER-positive tumours were similar between groups; 574 out of 716 (80.2%) and 580 out of 735 (78.9%) for the ZOLADEX and CMF arms, respectively.

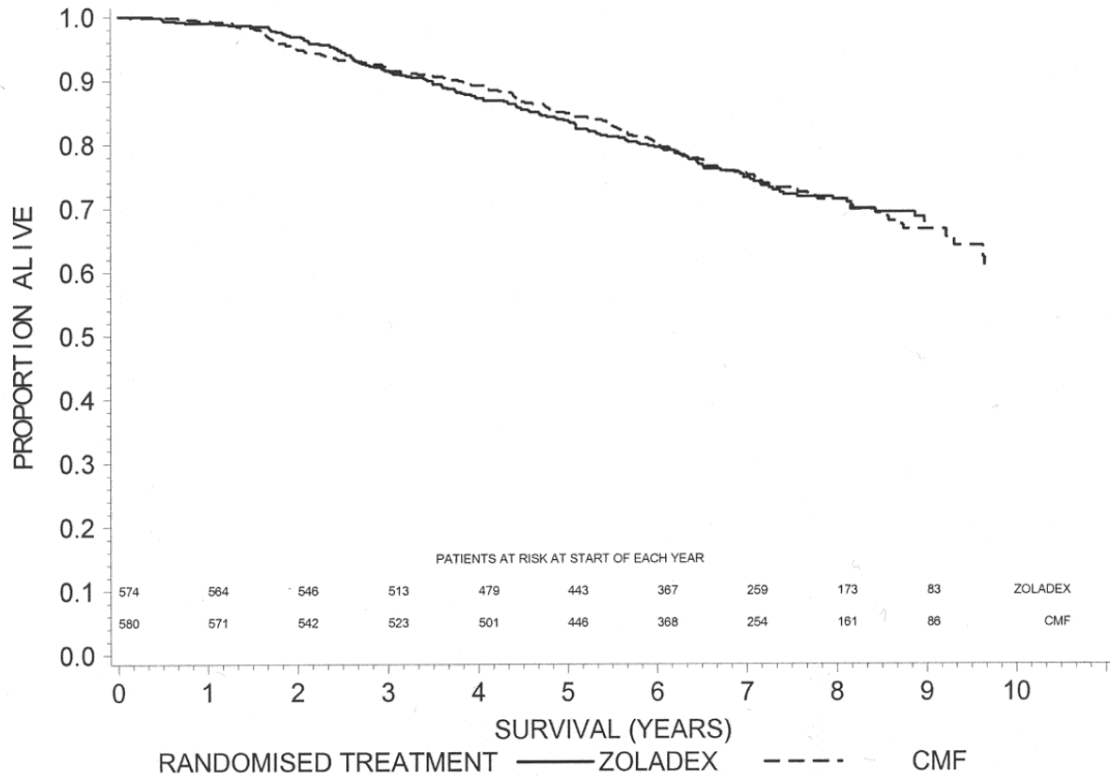
At a median follow-up time of 7.5 years, 395 (51%) patients in the ZOLADEX arm and 348 (44%) patients in the CMF arm had had an event (i.e., recurrence, second primary cancer, or death). In the Cox proportional hazards model used to analyze disease-free survival, the treatment by ER status interaction was highly significant ($p < 0.001$); ER-positive patients fared equally well regardless of trial treatment (i.e., ZOLADEX was equivalent to CMF) (Figure 3). However, patients with ER-negative tumours, or where ER status was unknown, fared better when treated with CMF.

Figure 3 ZEBRA Trial: Kaplan-Meier Disease-Free Survival - ER-Positive Patients



Results from the overall survival analysis, median follow-up time of 7.5 years, reflected the results for disease-free survival and indicate that ZOLADEX adjuvant therapy is at least as equivalent as CMF. In the ZOLADEX arm 147 (26%) patients and in the CMF arm 152 (26%) patients had died (Figure 4).

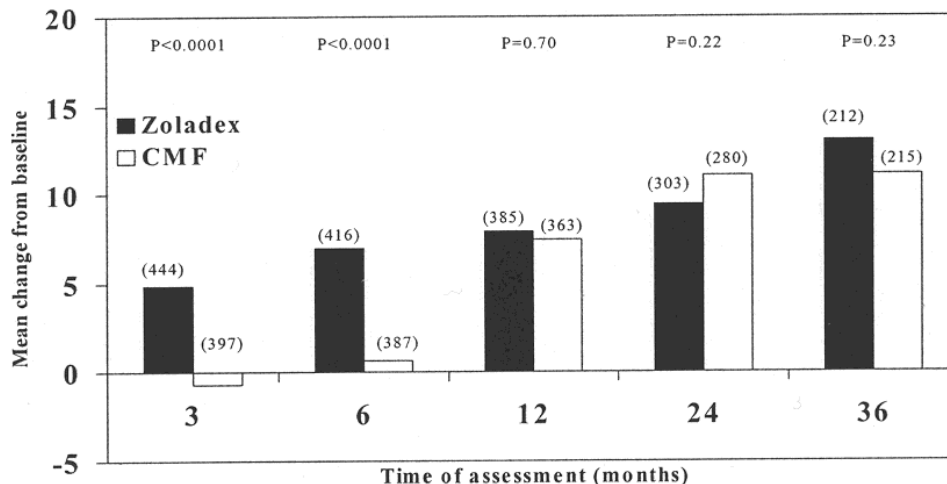
Figure 4 ZEBRA Trial: Kaplan-Meier Overall Survival - ER-Positive Patients



Up to 99.4% of patients became amenorrhoeic during the ZOLADEX treatment period, and one year following the end of the treatment period, the percentage had decreased to 23.9%.

The quality of life of patients receiving ZOLADEX was generally better than that of patients receiving CMF (e.g., physical symptom, activity level, ability to cope with illness, and overall quality of life scores) during the CMF treatment period due to the expected side effects of cytotoxic chemotherapy, e.g., nausea/vomiting and alopecia. The improvement in score for overall quality of life from baseline was significantly greater ($p < 0.0001$) in patients who received ZOLADEX compared to those who received CMF during the first 3-6 months. However, at 1 and 2 years when CMF patients had completed their treatment and while the ZOLADEX patients were still on active treatment, there were no significant differences observed between the two groups (Figure 5).

Figure 5 ZEBRA Trial: Score For Overall Quality Of Life (QoL) (least square mean)



Adjuvant Combination Therapy - ZOLADEX or ZOLADEX plus Tamoxifen Following Chemotherapy:

A supportive, open, randomized trial (INT0101) in premenopausal women with node-positive, hormone receptor-positive early breast cancer consisted of the following treatment groups: cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) for six 28-day cycles (n=510), CAF for six 28-day cycles followed by ZOLADEX 3.6 mg every 28 days for 5 years (CAF+Z) (n=511), or CAF for six 28-day cycles followed by ZOLADEX 3.6 mg every 28 days for 5 years plus tamoxifen 20 mg daily for 5 years (CAF+Z+T) (n=516). The median follow-up time was 7.1 years. An event, defined by a recurrence, second primary breast cancer or death, had occurred in 202 (39.6%) CAF patients, 183 (35.8%) CAF+Z patients, and 145 (28.1%) CAF+Z+T patients.

Analyses of disease-free survival indicated that patients benefited from receiving hormone therapy in addition to chemotherapy; differences approached or attained statistical significance (p=0.05) for patients who were randomized to CAF+Z or CAF+Z+T compared with patients who were randomized to CAF alone (Table 5). Analyses of overall survival also suggest a benefit for patients receiving hormone therapy and follow the trend of the results of the disease-free survival analyses, however, the differences were not statistically significant.

A subgroup analyses for disease-free survival by age suggests that for patients aged less than 40 years, there is an added therapeutic benefit with the addition of ZOLADEX or ZOLADEX plus tamoxifen following chemotherapy. In these younger women, five-year disease-free survival rates were 54% for CAF alone, 65% for CAF + Z and 72% for CAF + Z + T. The addition of hormone therapy may add to the potentially incomplete or suboptimal amenorrhea produced by chemotherapy alone.

Table 5 **Trial INT0101: Analyses of Disease-Free Survival (Primary Efficacy Population)**

Population/comparison	Hazard ratio^a	95% confidence interval	p-value
Primary efficacy population			
CAF vs CAF + Z	0.831	0.680, 1.017	0.073
CAF vs CAF + Z+T	0.618	0.498, 0.767	<0.001
CAF+Z vs CAF + Z+T	0.747	0.600, 0.931	0.009

^a A hazard ratio <1 indicates a better result for the second treatment group compared to the first treatment group.
CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil for six 28-day cycles.
CAF+Z: CAF for six 28-day cycles followed by ZOLADEX 3.6 mg every 28 days for 5 years.
CAF+Z+T: CAF for six 28-day cycles followed by ZOLADEX 3.6 mg every 28 days for 5 years plus tamoxifen 20 mg daily for 5 years.

DETAILED PHARMACOLOGY

Pharmacodynamics

Animal studies were undertaken to determine the endocrine and antitumour effects of goserelin acetate in both an aqueous and depot formulation.

A single subcutaneous injection of 500 µg goserelin acetate as an aqueous formulation suppressed estrus for only 3.4 ± 0.4 days in normally cycling rats. By comparison a single subcutaneous depot containing 500 µg goserelin acetate suppressed estrus for 33.2 ± 1.4 days. Single subcutaneous depots containing either 500 µg or 5 mg goserelin acetate decreased serum luteinizing hormone (LH) and testosterone and reduced testes, seminal vesicle and ventral prostate gland weights in rats for four weeks; there was no effect on the weight of the pituitary gland. Serum hormones and testes and accessory sex organ weights recovered between weeks 6 and 8 of the study.

Dimethylbenzanthracene (DMBA)-induced rat mammary tumours were reduced in size in response to a single subcutaneous injection of a depot containing 300 µg goserelin acetate.

Around seven weeks after administration of the drug, the tumours regrew but retained hormone-responsiveness and regressed again after either further treatment with a depot containing 300 µg goserelin acetate or surgical oophorectomy. Depot administration on three occasions at days 0, 28 and 56 caused a higher incidence of complete remission and a longer duration of effect. Both treatments markedly reduced the number of new tumours appearing during the study.

When given 30 days after DMBA, a single subcutaneous depot containing 300 µg goserelin acetate with repeat doses at 28-day intervals on two occasions caused a delay in tumour appearance of approximately 100 days. When given at 28-day intervals until the animals died or were killed, single subcutaneous depot doses of 300 µg goserelin acetate caused a

prolonged delay in mammary tumour appearance, and 12 out of 21 rats died or were killed without mammary tumours being detected.

Other Investigations

During the preclinical investigations of ZOLADEX, it was observed that rats treated with ZOLADEX had a higher incidence of pituitary adenomas than control animals. Because of these findings, pituitary CT scans in ZOLADEX treated and control patients from Phase III prostate cancer clinical studies were conducted.

In this investigation, no cases of definitive pituitary adenomata were found in evaluation of 164 pituitary CT scans. Findings in the long-term animal toxicology studies appear to represent a species-specific effect of castration in the rat. No relevance to humans has been established.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies were conducted in rats and mice. All animals survived following single subcutaneous doses of 200 mg/kg in rats and 400 mg/kg in mice. The LD50 by the subcutaneous route is, therefore, in excess of these values. The only signs reported were in the rats and are those related to discomfort of dosing. By the intravenous route LD50 was established at approximately 30-40 mg/kg for rats and 56-59 mg/kg for mice.

Long-term Toxicity

Multiple dosing studies have been conducted in rats, dogs and monkeys.

Six and 12 month studies were done in rats and dogs.

In the six month studies the doses were administered either as daily injections (aqueous solution) or depot injections every 28 days.

The doses used were up to 1000 µg/kg/day in rats and dogs by daily subcutaneous injections and, nominally, 150 µg/kg/day in rats and 200 µg/kg/day in dogs by depot injections every 28 days.

In the 12 month studies, only the depot injections were used and these provided maximal nominal dose levels of around 130 µg/kg/day in rats and 200 µg/kg/day in dogs.

In a monkey study 6 depot doses were administered, one every 28 days (providing approximately 400 µg/kg/day). At the end of this period a proportion of animals were necropsied and the remainder given a period of 6 months drug withdrawal to study reversibility.

Findings in all animal species were those of chemical castration as evidenced by reduced testicular size, suppression of estrus and histologic evidence of gonad and secondary sex

organ atrophy in both sexes. Pituitary gland microadenomas were observed only in rats; in 2 males in the depot group of the 6 month study and also in a larger proportion of dosed males in the 12 month study (see Carcinogenicity section for additional information).

Pregnancy, Teratogenic Effects

Administration of ZOLADEX led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action at 30-60 and 20-40 times the recommended human dose respectively. Except for the testes, almost complete histologic reversal of these effects in male and female rats was observed several weeks after dosing was stopped. Fertility and general reproductive performance was reduced in those that became pregnant after ZOLADEX was discontinued. Fertile matings occurred within two weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place. The ovulation rate, the corresponding implantation rate and number of live fetuses were reduced.

In male and female dogs, the suppression of fertility was fully reversible when drug treatment was stopped after continuous administration for 1 year at 100 times the recommended monthly dose.

Studies in both rats and rabbits (up to 25 and 500 times the monthly dose respectively) confirm that ZOLADEX will increase pregnancy loss in a dose-related manner. In both rats and rabbits, there was no evidence that ZOLADEX possessed the potential to cause teratogenicity.

Carcinogenicity

Compared to the control group animals an increased incidence of benign pituitary gland adenomas was found in male rats following long-term dosing in the carcinogenicity study where doses approximating to 60 and 120 µg/kg/day were administered every 28 days by depot injections. The chemical castration effect is responsible for the production of pituitary gland adenomas, which appears to be a species-specific response. This response is similar to that seen in surgically castrated rats. There were no pituitary gland adenomas observed in the mouse where large doses of the compound were administered (depot doses approximating to 1200 and 2400 µg/kg/day for 2 years). At the end of two years dosing in the mouse, findings of hyperplasia of the pancreatic islet cells and adenomatous polyps in pyloric stomach were reported but there was no evidence of carcinogenicity.

Extensive experience in human subjects with LHRH analogs, including goserelin acetate does not provide any evidence for a drug-related complication in the pituitary gland, stomach or pancreas. The findings discussed here are, therefore, unlikely to be relevant to the intended use in humans.

Mutagenicity

The mutagenic potential of the compound has been investigated in seven systems, five of them eukaryotic including two in vivo mammalian cell tests.

Tests for point mutation were done using the Salmonella typhimurium and Escherichia coli bacterial systems and Saccharomyces cerevisiae strain D7 yeast. Concentrations used were up to the limit of solubility (2000 µg/mL culture; 5000 µg/plate).

Clastogenic action on chromosomes was investigated in vivo using the mouse micronucleus test (2.5 mg and 5.0 mg/kg) and Chinese hamster bone marrow cytogenetics (15 mg/kg). For completion, two other in vitro mammalian cell culture tests (Chinese hamster ovary cells and human lymphocytes) were also done.

In none of these investigations was there any evidence of genotoxic potential.

Miscellaneous

Dermal tolerance was studied by direct application of a solution of goserelin acetate to the abraded and nonabraded skin of the rabbit. This produced no evidence of irritancy at a concentration of 10 mg/mL. A positive reference substance gave the appropriate response, thereby confirming the validity of the test system.

Ocular tolerance was established by instillation of 0.1 mL of a 10 mg/mL solution to the eyes of rabbits.

Contact sensitization was investigated in the guinea pig using a modified Magnusson and Kligman procedure. No sensitizing potential was detected, and the positive reference material gave the appropriate response.

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PART III: CONSUMER INFORMATION

Pr **Zoladex**[®]
goserelin depot

This leaflet is part III of a three-part "Product Monograph" published when ZOLADEX[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZOLADEX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What ZOLADEX is used for:

Prostate Cancer

ZOLADEX is used:

- For the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate (Stage D2).
- In combination with a non-steroidal antiandrogen and radiation therapy for the management of locally advanced (T3, T4) or bulky Stage T2b, T2c carcinoma of the prostate.
- As adjuvant hormone therapy to external beam irradiation for patients with locally advanced prostate cancer (Stage T3-T4).

Breast Cancer

ZOLADEX is used:

- As an alternative to standard adjuvant chemotherapy in pre- and perimenopausal women with early breast cancer who are unsuitable for, intolerant to, or decline chemotherapy, and whose tumour contains estrogen and/or progesterone receptors.
- ZOLADEX is indicated for the palliative treatment of advanced breast cancer in pre- and perimenopausal women whose tumour contains estrogen and/or progesterone receptors.

Benign Conditions

ZOLADEX is indicated for the hormonal management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with ZOLADEX for the management of endometriosis has been limited to women 18 years of age and older, treated for 6 months.

ZOLADEX is indicated for use as an endometrial thinning agent prior to endometrial ablation.

What ZOLADEX does:

ZOLADEX treatment, given once every 28 days, results in suppression of your sex hormones (testosterone in men and estradiol in women).

When ZOLADEX should not be used:

You should not use ZOLADEX if:

- You are allergic to goserelin acetate or any nonmedicinal ingredients of in ZOLADEX.
- You are a woman who has abnormal vaginal bleeding for an unknown reason.
- You are a woman who is pregnant.
- You are a woman who is breastfeeding.

What the medicinal ingredient is:

goserelin acetate

What the important nonmedicinal ingredients are:

Lactide-glycolide copolymer

What dosage forms ZOLADEX comes in:

ZOLADEX comes in a hard, cream-coloured, rod-shaped depot which contains 3.6mg goserelin as goserelin acetate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZOLADEX should be prescribed and managed by a doctor experienced with using this type of drug.

ZOLADEX should be administered by a healthcare professional experienced in administering deep subcutaneous injections and under the supervision of a physician.

ZOLADEX may cause:

- Worsening of symptoms of prostate cancer at the beginning of the treatment (risk of spinal cord compression, or increased difficulty in urinating)
- Bone thinning (osteoporosis)
- Injection site injury (including damage to blood vessels in the abdomen) has been reported following injection of ZOLADEX. In rare cases this has caused severe bleeding (with some cases requiring surgical treatment).

If you go into hospital, let the medical staff know you are receiving ZOLADEX.

In women, there are no clinical data on the effect of treating endometriosis with ZOLADEX for periods in excess of 6 months.

ZOLADEX is not recommended for use in children.

ZOLADEX is not recommended for use in very thin patients and/or those on blood thinners.

ZOLADEX is unlikely to affect your ability to drive a car or to operate machinery.

Before you use ZOLADEX, talk to your doctor or pharmacist if any of the following applies to you:

- Have or have had any problems passing urine.
- Family history of severe osteoporosis (thinning of the bones with fractures).
- Have low bone mineral density (BMD).
- Taking other medicines that cause thinning of the bones.
- Have a low red blood cell count (anemia)
- Have heart or blood vessel disease, have had an abnormal heart rhythm (QT prolongation), have a heart condition called ‘long QT syndrome’, a family history of this heart condition, or are being treated with medicines for these conditions. ZOLADEX may increase the risk of having an abnormal heart rhythm (QT prolongation).
- Have diabetes
- Are pregnant or planning to become pregnant. ZOLADEX should not be used during pregnancy, therefore, effective non-hormonal contraceptive methods should be used to prevent pregnancy during the treatment and until the return of menses after the last injection with ZOLADEX. After stopping ZOLADEX it may take longer for some women to experience menses. Rarely, some women may enter menopause. If 8 weeks have passed after the last ZOLADEX injection and you do not experience menses, talk to your doctor.
- Taking blood thinners.

- It is very important your doctor checks your progress at regular medical visits. Consult your doctor before you decide to change your treatment.
- If you need more information, ask your doctor.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you missed your scheduled dose, contact your doctor for advice.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects are sometimes experienced with ZOLADEX.

Contact your doctor or pharmacist if you experience any of these problems:

- Tingling in your fingers or toes.
- Psychiatric problems such as hallucinations, disordered thoughts or personality change. These have occasionally been reported.
- Injection site injury (including damage to blood vessels in the abdomen) has been reported following injection of ZOLADEX. This can cause severe bleeding. Contact your doctor immediately if you experience any of the following symptoms: bleeding underneath the skin or bruising, abdominal pain, abdominal distension, swelling at the injection site, shortness of breath, dizziness, low blood pressure and/or any altered levels of consciousness.
- There have been occasional reports of side effects with pituitary tumours. You may develop a tumour of the pituitary gland in your head or, if you have an existing tumour of the pituitary gland, ZOLADEX may cause it to bleed or collapse. Pituitary tumours may cause headaches, vomiting, loss of eyesight and unconsciousness.
- A local skin reaction may occur at the injection site such as pain, bruising, bleeding, itching, redness, burning and swelling. These reactions generally are mild and disappear after a few days. If they get worse or do not go away, tell your doctor.
- **Cancer patients:** Contact your doctor immediately if you develop: severe increased pain, numbness or weakness of the limbs, or persistent difficulty in urinating (prostate cancer).

INTERACTIONS WITH THIS MEDICATION

Check with your doctor or pharmacist before taking any other drugs, including non-prescription drugs (for colds, nausea, etc.). ZOLADEX might interfere with some medicines used to treat heart rhythm problems or might increase the risk of heart rhythm problems when used with some other drugs that can cause heart rhythm abnormalities.

PROPER USE OF THIS MEDICATION

Usual Dose

- ZOLADEX is given as an injection under the skin of the abdomen by a trained health care professional, such as a doctor or nurse.
- **Prostate or breast cancer:** one injection every 28 days.
- **Endometriosis:** one injection every 28 days.

Use of ZOLADEX in Men

- When you first start receiving ZOLADEX you may feel some pain in your bones. If this happens tell your doctor and you may be given something for this.
- Very occasionally you may have trouble passing urine or experience lower back pain. If this happens, tell your doctor and you may be given something for this.
- You may experience hair loss, particularly the loss of body hair.

Use of ZOLADEX in Women

- For pre-menopausal women: menstruation stops with the monthly depot of ZOLADEX. If regular menstruation persists, notify your doctor. If a monthly ZOLADEX depot is missed, breakthrough menstrual bleeding may occur.
- Vaginal bleeding may occur. At the beginning of treatment, if you have fibroids a slight increase in symptoms, such as pain, may occur. These effects are usually short-lived and discontinue on continuation of treatment. If symptoms persist or you are uncomfortable, contact your doctor.
- Occasionally some women may enter menopause early, so when ZOLADEX treatment is stopped, menstruation will not start again.
- ZOLADEX has been associated with the formation of ovarian cysts, which may cause pain for some women.
- If you experience excessive nausea, vomiting or thirst, you should tell your doctor. This may indicate possible changes in the amount of calcium in your blood and your doctor may have to do certain blood tests.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
USE OF ZOLADEX IN MEN			
Very Common (more than 10 in every 100 patients are likely to have them)			
Reduced sex drive/impotence	√		
Hot flushes and sweating	√		
Common (1 to 10 in every 100 patients are likely to have them)			
Change in breast size	√		
Injection site reaction	√		
Depression		√	
Bone pain	√		
Rises in blood sugar levels		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Tingling in fingers or toes	√		
Changes in blood pressure		√	
Skin rashes	√		
Thinning of bones		√	
Heart failure (reduced heart function) or heart attack		√	
Weight gain	√		
Uncommon (1 to 10 in every 1000 patients are likely to have them)			
Tender breasts	√		
Joint pain		√	
Allergic reactions		√	
Rare (1 to 10 in every 10 000 patients are likely to have them)			
Severe bleeding due to injection site injury, including damage to blood vessels in the abdomen. Symptoms such as bleeding underneath the skin or bruising, abdominal pain, abdominal distension, swelling at the injection site, shortness of breath, dizziness, low blood pressure and/or altered levels of consciousness.		√	
USE OF ZOLADEX IN WOMEN			
Very Common (more than 10 in every 100 patients are likely to have them)			
Reduced sex drive	√		
Hot flushes and sweating	√		
Vaginal dryness	√		
Change in breast size	√		
Injection site reaction	√		
Acne*	√		
Common (1 to 10 in every 100 patients are likely to have them)			
Increased signs and symptoms of breast cancer		√	
Mood changes including depression		√	
Tingling in fingers and toes	√		
Headache		√	
Changes in blood pressure		√	
Skin rashes	√		
Thinning of bones		√	
Joint pain		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Hair loss (usually mild but occasionally severe)	√		
Weight gain	√		
Uncommon (1 to 10 in every 1000 patients are likely to have them)			
Allergic reactions		√	
Rare (1 to 10 in every 10 000 patients are likely to have them)			
Severe bleeding due to injection site injury, including damage to blood vessels in the abdomen. Symptoms such as bleeding underneath the skin or bruising, abdominal pain, abdominal distension, swelling at the injection site, shortness of breath, dizziness, low blood pressure and/or altered levels of consciousness.		√	

* Often, acne is reported within one month after starting ZOLADEX.

This is not a complete list of side effects. For any unexpected effects while taking ZOLADEX, contact your doctor or pharmacist.

HOW TO STORE IT

- ZOLADEX should not be used after the expiry date on the pack. Store ZOLADEX in its original pack between 2°C and 25°C.
- If your doctor decides to stop your treatment, return ZOLADEX to the pharmacy for proper disposal.
- Keep your ZOLADEX in a safe place where children cannot reach it. It could harm them.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION Leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information leaflet, plus the full Product Monograph prepared for health professionals can be found at:

www.tersera.ca, or by contacting the sponsor at: Questions or concerns – 1-855-820-2141

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