

PRODUCT MONOGRAPH

PZOLADEX[®] LA

Goserelin Depot

10.8 mg Goserelin/depot
(as goserelin acetate)

Luteinizing Hormone - Releasing Hormone Analog
(LHRH Analog)

TerSera Therapeutics LLC
Lake Forest, IL 60045
www.tersera.ca

Importer:
AstraZeneca Canada Inc.
Mississauga, Ontario L4Y 1M4

Date of Revision:
December 21, 2017

Submission Control No. 210199

ZOLADEX[®] and SAFESYSTEM[®] are registered trademarks of AstraZeneca or its affiliates and are used herein under license.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	9
DRUG INTERACTIONS.....	15
DOSAGE AND ADMINISTRATION	16
OVERDOSAGE.....	19
ACTION AND CLINICAL PHARMACOLOGY	20
STORAGE AND STABILITY	22
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	22
PART II: SCIENTIFIC INFORMATION.....	23
PHARMACEUTICAL INFORMATION	23
DETAILED PHARMACOLOGY	23
TOXICOLOGY.....	25
REFERENCES.....	28
PART III: CONSUMER INFORMATION.....	34

PrZOLADEX® LA

Goserelin Depot

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Depot/10.8 mg goserelin	Lactide-glycolide copolymer <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Prostate Cancer

- ZOLADEX LA (goserelin acetate) 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 LA 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 LA and a non-steroidal antiandrogen should start 8 weeks prior to initiating radiation therapy and continue until completion of the radiation therapy.
- ZOLADEX LA as adjuvant hormone therapy to external beam irradiation for patients with locally advanced prostate cancer (Stage T3-T4).

Benign Conditions

- ZOLADEX LA 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.

Pediatrics:

The safety and effectiveness of ZOLADEX LA 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 LA should not be used during pregnancy. As with other LHRH agonists it is not known whether ZOLADEX LA 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 LA during breast feeding is not recommended.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

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

ZOLADEX LA 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 LA. Monitor patients for signs or symptoms of abdominal hemorrhage. As

ZOLADEX LA 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 LA transiently increases serum testosterone in males and serum estradiol concentrations in females. 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.

In women, ZOLADEX LA is only indicated for use in endometriosis. For female patients requiring treatment with goserelin for other conditions, refer to the prescribing information for ZOLADEX (3.6 mg depot).

Effect on ability to drive a vehicle and use machinery: There is no evidence that ZOLADEX LA 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 LA, 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 LA, 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 LA.

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 LA. 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.

While specific data from the use of ZOLADEX LA are not currently available, 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 LA may pose an additional risk. In these patients the risks and benefits must be weighed carefully before ZOLADEX LA therapy 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 LA. Initially, ZOLADEX LA like other LHRH agonists transiently increases serum testosterone concentrations. 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 3 months. 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 LA 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 LA 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 12 weeks after the last dose of ZOLADEX LA. 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 LA 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 LA, 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 LA has not been established.

The use of ZOLADEX LA may cause an increase in cervical resistance and care should be taken when dilating the cervix.

Special Populations

Pregnant Women: ZOLADEX LA 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 LA during breast feeding is not recommended.

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

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

Monitoring and Laboratory Tests

Monitoring of patients

During therapy with ZOLADEX LA, 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 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.

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.

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.

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 LA.

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 LA 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 LA results in suppression of pituitary-gonadal system. Diagnostic tests of pituitary-gonadal function conducted during and subsequent to the treatment period may therefore be misleading.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse effects seen with ZOLADEX LA (goserelin acetate) are due primarily to its pharmacological 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. 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 tumour 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 LA. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with ZOLADEX LA. Such changes have rarely required medical intervention including withdrawal of ZOLADEX LA 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 (1.9%) in patients after the first 12 weeks following ZOLADEX LA administration 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 LA). Common adverse reactions ($\geq 1\%$ to $<10\%$) are: mood alteration including depression, headache, arthralgia and tumour flare/tumor pain. Rare ($\geq 0.01\%$ to $<0.1\%$) cases of ovarian cyst have been reported. At the beginning of ZOLADEX LA 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 LA, 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 LA.

Clinical Trial Adverse Drug Reactions

Prostate Cancer Patients

Pharmacological effects include hot flush, hyperhidrosis and erectile dysfunction, seldom requiring withdrawal of therapy. Gynecomastia and breast tenderness have been noted infrequently. Initially, prostate cancer patients may experience a temporary increase in bone

pain, which can be managed symptomatically. Isolated cases of spinal cord compression have been recorded.

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). Following the administration of ZOLADEX 3.6 mg depot, isolated cases of ureteric obstruction have been recorded.

Two controlled clinical trials were conducted with 157 patients, comparing treatment with ZOLADEX LA (10.8 mg) versus ZOLADEX 3.6 mg depots. During the comparative phase, patients were randomised to receive either a single 10.8 mg depot or three consecutive 3.6 mg depots (one every 4 weeks) over this initial 12 week period. The only adverse event reported in greater than 5% of these patients during this phase, was hot flush, with the ZOLADEX LA (10.8 mg) group having an incidence of 47% and the ZOLADEX 3.6 mg group having 48%.

From weeks 12-48 all patients were treated with one ZOLADEX LA depot every 12 weeks. During this noncomparative phase, the following adverse events, were reported in greater than 5% of patients; hot flush [vasodilation] (63.7%), general pain (14%), gynaecomastia (8.3%), pelvic pain (5.7%), bone pain (5.7%) and asthenia (5.1%).

The following adverse events reported in greater than 1%, but less than 5% of 157 patients treated with ZOLADEX LA depot every 12 weeks are tabulated below. Some of these would be expected in a proportion of the elderly population.

Table 1 Adverse events in controlled studies with an incidence of $\geq 1\%$ but less than 5%

Body system/adverse events	Weeks 0 to 12		Week 12 onwards	
	ZOLADEX 10.8mg (N = 78)		ZOLADEX 10.8 mg (N = 157)*	
	N	(%)	N	(%)
<i>Whole Body</i>				
Abdominal pain	0	(0.0)	2	(1.3)
Aggravation reaction	0	(0.0)	5	(3.2)
Back pain	0	(0.0)	2	(1.3)
Flu syndrome	1	(1.3)	0	(0.0)
Headache	0	(0.0)	3	(1.9)
Infection	0	(0.0)	2	(1.3)
Sepsis	0	(0.0)	4	(2.5)
<i>Cardiovascular</i>				

Body system/adverse events	Weeks 0 to 12		Week 12 onwards	
	ZOLADEX 10.8mg (N = 78)		ZOLADEX 10.8 mg (N = 157)*	
	N	(%)	N	(%)
Angina pectoris	1	(1.3)	1	(0.6)
Cerebral ischemia	0	(0.0)	2	(1.3)
Cerebrovascular accident	0	(0.0)	2	(1.3)
Heart failure	0	(0.0)	3	(1.9)
Pulmonary embolus	0	(0.0)	2	(1.3)
Varicose veins	1	(1.3)	0	(0.0)
<i>Digestive</i>				
Diarrhoea	1	(1.3)	4	(2.5)
Hematemesis	1	(1.3)	0	(0.0)
<i>Endocrine System</i>				
Diabetes mellitus	0	(0.0)	2	(1.3)
<i>Hemic and Lymphatic</i>				
Anaemia	0	(0.0)	3	(1.9)
<i>Metabolic and Nutritional</i>				
Peripheral oedema	2	(2.6)	5	(3.2)
<i>Nervous System</i>				
Dizziness	0	(0.0)	5	(3.2)
Paraesthesia	2	(2.6)	2	(1.3)
Urinary retention	0	(0.0)	2	(1.3)
<i>Respiratory system</i>				
Cough increased	0	(0.0)	4	(2.5)
Dyspnoea	0	(0.0)	6	(3.8)
Pneumonia	0	(0.0)	2	(1.3)
<i>Skin Appendages</i>				
Herpes simplex	1	(1.3)	1	(0.6)
Pruritus	0	(0.0)	2	(1.3)
<i>Urogenital</i>				
Bladder neoplasm	1	(1.3)	1	(0.6)
Breast pain	2	(2.6)	7	(4.5)

Body system/adverse events	Weeks 0 to 12		Week 12 onwards	
	ZOLADEX 10.8mg (N = 78)		ZOLADEX 10.8 mg (N = 157)*	
	N	(%)	N	(%)
Hematuria	1	(1.3)	3	(1.9)
Impotence	2	(2.6)	2	(1.3)
Urinary frequency	0	(0.0)	2	(1.3)
Urinary incontinence	0	(0.0)	2	(1.3)
Urinary tract disorder	1	(1.3)	5	(3.2)
Urinary tract infection	3	(3.8)	7	(4.5)
Urination Impaired	0	(0.0)	3	(1.9)

* Adverse events occurring in the comparative phase of these studies (Weeks 0 to 12) are presented separately to data from the non-comparative phase (Week 12 onwards), as the differences in the two periods of observation made a direct comparison inappropriate.

In a controlled clinical trial conducted with 58 patients, ZOLADEX LA 10.8 mg was administered every 13 weeks (3 months). Adverse events were consistent with the results of earlier trials. The following adverse events were reported in 10% or more patients; hot flush [vasodilation] (67%), general pain (31%), pelvic pain (22%), back pain (16%), insomnia (16%), hyperhidrosis (14%), hypertension (12%), constipation (12%), urinary frequency (12%), and nocturia (10%).

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 2 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

	(n=294) Flutamide + LHRH-agonist % All	(n=285) Placebo + LHRH-agonist % All
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other GI	6	4

As shown in Table 2, 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.

Benign Conditions

Pharmacological effects of ZOLADEX LA treatment in women include hot flush and hyperhidrosis, and decreased libido, seldom requiring withdrawal from therapy. Headaches, mood alteration including depression, vulvovaginal dryness and breast enlargement have been noted infrequently.

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

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 LA 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.

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

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

As ZOLADEX LA 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

Prostate Cancer

One depot of ZOLADEX LA containing goserelin acetate equivalent to 10.8 mg goserelin, should be injected subcutaneously into the anterior abdominal wall every 3 months (**13 weeks**) following the procedure recommended in the administration instructions (see-Directions for Use attached to sterile pouch). While the 3-month (**13 week**) schedule should be adhered to, a delay of a few days is permissible (See DETAILED PHARMACOLOGY).

If in exceptional circumstances repeat dosing does not occur at 3 months, data indicate that castrate levels of testosterone are maintained for up to 16 weeks in the majority of patients.

When ZOLADEX LA 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 until completion of the radiation therapy, can be administered.

Endometriosis

One depot of ZOLADEX LA containing goserelin acetate equivalent to 10.8 mg goserelin, should be injected subcutaneously into the anterior abdominal wall every 12 weeks following the procedure recommended in the administration instructions (see-Directions for Use attached to sterile pouch). While the 12-week schedule should be adhered to, a delay of a few days is permissible (See DETAILED PHARMACOLOGY).

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). When ZOLADEX LA is given, as recommended, this change will not lead to any accumulation hence, no change in dosing is necessary for patients with renal failure.

Hepatic Impairment

Hepatic impairment does not compromise the clearance of ZOLADEX LA, 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 LA in children has not been established. (See WARNINGS AND PRECAUTIONS).

Administration

ZOLADEX LA is administered by deep subcutaneous injection into the anterior abdominal wall below the navel line. Caution should be taken while injecting ZOLADEX LA 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.**

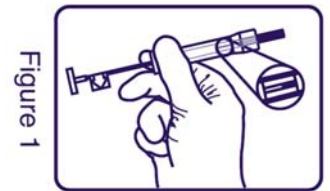
ZOLADEX LA 10.8 mg Step by Step Directions for Use

ZOLADEX LA should be administered using an aseptic technique.

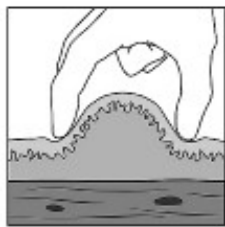
1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare an area of the anterior abdominal wall below the navel line with an alcohol swab.

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

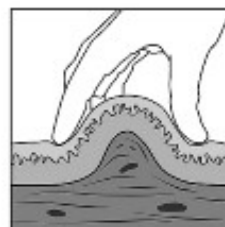
2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light. Check that at least part of the ZOLADEX LA depot is visible (**Figure 1**).
3. Grasp the plastic safety tab and pull away from the syringe and discard (**Figure 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 LA 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 LA depot may be injected with a new syringe elsewhere. The use of ZOLADEX LA 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 LA 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 LA depot, it may be localized by ultrasound.

OVERDOSAGE

The pharmacologic properties of ZOLADEX LA (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 LA 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 LA (goserelin acetate) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH or LHRH). When given acutely, goserelin acetate stimulates the release of pituitary 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.

In men, approximately 21 days after the initiation of therapy, a sustained suppression of pituitary LH results in the reduction in serum testosterone levels to a range normally seen in surgically castrated men. This suppression of testosterone is then maintained on repeat administration of ZOLADEX LA as long as therapy is continued.

In women, serum estradiol concentrations are suppressed by around 4 weeks after the first depot injection and remain suppressed, at levels comparable with those observed in postmenopausal women, until the end of the treatment period. In patients with estradiol already suppressed by an LHRH analogue, suppression is maintained on the change of therapy to ZOLADEX LA. Suppression of estradiol is associated with a response in endometriosis and will result in amenorrhea in the majority of patients. During early treatment with ZOLADEX LA 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 12 weeks after the last dose of ZOLADEX LA.

ZOLADEX LA 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.

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

ZOLADEX LA is poorly protein bound and has a serum elimination half-life 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 since, for the compound given, as recommended, in a 10.8 mg depot formulation, this change will not lead to any accumulation, no change in dosing is necessary in these patients. There is no significant change in the clearance of ZOLADEX LA in patients with hepatic impairment with normal renal function (see Pharmacokinetics).

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 LA like other LHRH agonists transiently increases serum testosterone concentrations.

In men by around 21 days after the first ZOLADEX LA depot injection, testosterone concentrations have typically fallen to within the castrate range and remain suppressed with treatment every 3 months. In clinical trials using ZOLADEX LA for 48 weeks, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy. Data exists which indicates that in the majority of patients (over 90%), serum testosterone levels remain suppressed to within the castrate range for up to 13 weeks (3 months).

In women, serum estradiol concentrations are suppressed by around 4 weeks after the first depot injection and remain suppressed until the end of the treatment period. In patients with estradiol already suppressed by an LHRH analogue, suppression is maintained on the change of therapy to ZOLADEX LA. Suppression of estradiol is associated with a response in endometriosis and will result in amenorrhoea in the majority of patients.

Pharmacokinetics

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

ZOLADEX LA 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 LA in patients with hepatic impairment with normal renal function. The ZOLADEX LA (10.8 mg) depot formulation of goserelin acetate releases drug continuously with peak serum concentrations occurring approximately two hours after administration.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of ZOLADEX LA in children has not been established (see WARNINGS AND PRECAUTIONS).

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 LA,

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 LA 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 LA (goserelin acetate) depot is supplied as a cylindrical rod of biodegradable and biocompatible D-L Lactide-glycolide copolymer. Each ZOLADEX LA depot contains goserelin acetate equivalent to 10.8 mg of goserelin. This depot is presented in a sterile ready-to-use syringe with a 14 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 are attached.

Active Constituent: goserelin acetate equivalent to 10.8 mg goserelin per depot.

Other Constituents: Lactide-glycolide copolymer to total weight 36.0 mg per depot.

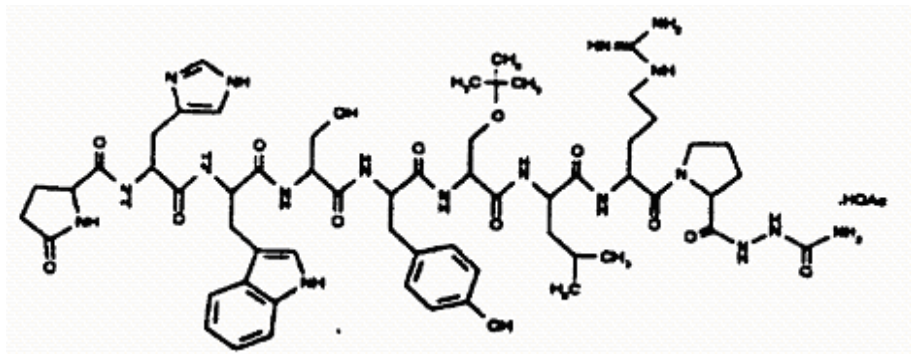
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Goserelin acetate
Chemical Name:	L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-(O-tert-butyl)seryl- L-leucyl-L-arginyl-L-prolyl-azaglycine amideacetate
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:



Physicochemical 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 pKa (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.

DETAILED PHARMACOLOGY

Where applicable, the following DETAILED PHARMACOLOGY information has been supplemented with information generated to support use of the ZOLADEX 3.6 mg depot, which is relevant to ZOLADEX LA.

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

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

In mice, long-term repeated dosing with multiples of the human dose produced histological changes in some regions of the digestive system. This is manifested by pancreatic islet cell hyperplasia and a benign proliferative condition in the pyloric region of the stomach, also reported as a spontaneous lesion in this species. The clinical relevance of these findings is unknown.

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.

REFERENCES

Endometriosis References

Barbieri RL.

Hormonal therapy of endometriosis. *Infertility and Reproductive Medicine Clinics of North America* 1992;3:187-200.

Howell R et al.

Gonadotrophin-releasing hormone analogue (goserelin) plus hormone replacement therapy for the treatment of endometriosis. *Fertility and Sterility* 1995;64(3):474-481.

Killholma P et al.

Comparison of the gonadotrophin-releasing hormone agonist goserelin combined with estrogen-progestogen add-back therapy in the treatment of endometriosis. *Fertility and Sterility* 1995; 64:903-908.

Rock JA, Truglia JA, Caplan RJ.

Zoladex (Goserelin Acetate Implant) in the treatment of endometriosis: a randomised comparison with Danazol. *Obstet Gynae* 1993;82(2):198-205.

Shaw RW.

An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. *Fertility and Sterility* 1992;58(2):265-272.

Sutton CJG, Ewen SP, Whitelaw N, Haines P.

Prospective, randomized, double-blind, controlled trial of laser laparoscopy in treatment of pelvic pain associated with minimal, mild and moderate endometriosis. *Fertility and Sterility* 1994;62:696-700.

Prostate Cancer References

Ahmann FR, Citrin DL, deHaan HA, Guinan P, Jordan V, Kreis W, et al.

Zoladex: a sustained-release, monthly luteinizing hormone-releasing hormone analogue for the treatment of advanced prostate cancer. *J Clin Oncol* 1987;5(6):912-7.

Anderson M, Capen C.

Hypertrophy and hyperplasia of the pituitary benign and malignant tumours of the pituitary. In: Benirschke K, Garner FM, Jane TC, editors. *Pathology of laboratory animals*. Berlin: Springer Verlag, 1978:I:430-2.

Anonymous.

Prostate cancer. Report of a meeting of physicians and scientists, Institute of Cancer Research and the Royal Marsden Hospital. *Lancet* 1993;342(8876):901-5.

Barsoum NJ, Moore JD, Gough AW, Sturgess JM, De La Iglesia FA.
Morphofunctional investigations on spontaneous pituitary tumors in wistar rats. *Toxicol Pathol* 1985;13(3):200-8.

Bergman B, Damber JE, Tomic R.
Effects of total and subcapsular orchidectomy on serum concentrations of testosterone and pituitary hormones in patients with carcinoma of the prostate. *Urol Int* 1982;37(2):139-44.

Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al.
Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337(5):295-300.

Bostwick D, Myers R and Oesterling J.
Staging of prostate cancer. *Semin Surg Oncol* 1994;10:60-72.

Cassileth BR, Soloway MS, Vogelzang NJ, Chou JM, Schellhammer PD, Seidmon EJ, et al.
Quality of life and psychosocial status in stage D prostate cancer. *Qual Life Res* 1992;1: 323-9.

Chrisp P, Goa KL.
Goserelin. A review of its pharmacodynamic and pharmacokinetic properties, and clinical use in sex hormone-related conditions. *Drugs* 1991;41(2):254-88.

Debruyne FM, Dijkman GA, Lee DCH, Witjes PJ.
A new long acting formulation of the luteinizing hormone-releasing hormone analogue, goserelin: results of studies in prostate cancer. *J Urol* 1996;155:1352-4.

Dearnaley DP.
Prostate cancer. *Lancet* 1993;342:901-905.

Deghenghi R, Misset JL.
Disease flare induced by luteinising hormone releasing hormone analogues in cancer patients. *Lancet* 1984;1(8389):1302.

Dijkman GA, Fernandez del Moral P, Plasman JW, Kums JJ, Delaere KP, Debruyne FM, et al.
A new extra long acting depot preparation of the LHRH analogue Zoladex. First endocrinological and pharmacokinetic data in patients with advanced prostate cancer. *J Steroid Biochem Mol Biol* 1990;37(6):933-6.

Dijkman GA, Fernandez del Moral P, Plasman JW, Pull HC, van der Meijden AP, Debruyne FM, et al.
A new longer-acting LHRH analog depot: preliminary results of a Dutch open phase II clinical study on a 10.8 mg Zoladex 3-monthly depot. *Eur Urol* 1990;18(suppl 3):22-5.

Doniach I.

The pathology of adenomas of the pituitary gland. In: Williams ED, editor. Current endocrine concepts. Eastbourne: Praeger, 1982:205-31.

Donnelly RJ, Milsted RAV.

Zoladex studies in prostatic and breast cancer. In: Vickery BH, Nestor JJ, editors. LHRH and its analogs; contraceptive and therapeutic applications, Part 2. Macclesfield: ICI Pharmaceuticals, 1987:397-409.

Furr BJ, Nicholson RI.

Use of analogues of luteinizing hormone-releasing hormone for the treatment of cancer. J Reprod Fertil 1982;64(2):529-39.

Furr BJ, Woodburn JR.

Luteinizing hormone-releasing hormone and its analogues: a review of biological properties and clinical issues. J Endocrinol Invest 1988;11(7):535-57.

Furth J, Nakane P, Pasteels JL.

Tumours of the pituitary gland. In: Turusov VS, editor. Pathology of tumours in laboratory animals, 1, Part 2. Lyon: IARC Scientific Publications, 1976:201-38.

Garnick M., Pratt C., Campion M., Shipley J., Bemardy J.D

Increase in the Electrocardiographic QTC Interval in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: Results of Three Randomised Controlled Clinical Studies. Eur Urol Suppl 2004 3(2):57

Grant JB, Ahmed SR, Shalet SM, Costello CB, Howell A, Blacklock NJ.

Testosterone and gonadotrophin profiles in patients on daily or monthly LHRH analogue ICI 118630 (Zoladex) compared with orchiectomy. Br J Urol 1986;58(5):539-44.

Griesbach WE, Purves HD.

Basophil adenoma in the rat hypophysis after gonadectomy. Br J Cancer 1960;14:49-59.

Harnois C, Malenfant M, Dupont A, Labrie F.

Ocular toxicity of Anandron in patients treated for prostatic cancer. Br J Ophthalmol 1986;70(6):471-3.

Jacobi GH.

Hormonal treatment of metastatic carcinoma of the prostate. In: Fitzpatrick JM, Kane RJ, editors. The prostate. New York: Churchill Livingstone, 1989:389-99.

Kaisary AV, Tyrrell CJ, Peeling WB, Griffiths K.

Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma. Br J Urol 1991;67(5):502-8.

Krane R, Fitzpatrick JM.

Treatment options for prostatic carcinoma. In: Fitzpatrick JM, Kane RJ, editors. The prostate. New York: Churchill Livingstone, 1989:433-9.

Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, Milani RV, Sagalowsky AI, Smith MR, Zakai N.

American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation*. 2010 Feb 16;121(6):833-40. Epub 2010 Feb 1. PubMed PMID: 20124128.

Lunglmayr G, Girsch E.

Patient choice in the treatment of advanced prostate cancer. In: Chisholm GD, editor. Zoladex - a new treatment for prostatic cancer. Royal Society of Medical Services International Congress and Symposium Series No. 125; Proceedings of a symposium, 1987 Apr 23; London, 1987:47-53.

MacFarlane JR, Tolley DA.

Flutamide therapy for advanced prostatic cancer: a phase II study. *Br J Urol* 1985;57(2):172-4.

Newling DWW, Denis L, Mahler C, Debruyne FMJ, Lunglmayr G, Robinson MRG, et al. Clinical and endocrinological results with a biodegradable depot LHRH analogue (Zoladex) in the management of advanced prostatic cancer. In: Chisholm GD, editor. Zoladex - a new treatment for prostatic cancer. Royal Society of Medical Services International Congress and Symposium Series No. 125; Proceedings of a symposium, 1987 Apr 23; London, 1987:17-26.

Peeling WB.

A phase III trial comparing ICI 118,630 (Zoladex) with orchidectomy in the management of advanced prostatic cancer. In: Chisholm GD, editor. Zoladex - a new treatment for prostatic cancer. Royal Society of Medical Services International Congress and Symposium Series No. 125; Proceedings of a symposium, 1987 Apr 23; London, 1987:27-46.

Perren TJ, Clayton RN, Blackledge GRP, Arkell D, Cottam J, Farrar D, et al. A pharmacokinetic, endocrine and clinical study of the LHRH analogue

DSER(tBU)⁶AZAGLY¹⁰GnRH (ICI 118,630) [abstract]. *Br J Cancer* 1985;52:499.

Pilepich MV, Krall JM, Al-Sarraf M, John MJ, Doggett ML, Sause WT, et al.

Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 1995;45(4):616-23.

Pierrepont CG, Turkes AO, Walker KJ, Harper ME, Wilson DW, Peeling WB, et al.

Endocrine factors in the treatment of prostatic cancer. *Prog Clin Biol Res* 1985;185A:51-72.

Saini A, Waxman J.

Recent progress in the treatment of advanced prostatic cancer. *Br J Hosp Med* 1992;47(2):122,125-6.

Sarosdy MF, Schellhammer PF, Soloway MS, Vogelzang NJ, Crawford ED, Presti J, et al. Endocrine effects, efficacy and tolerability of a 10.8-mg depot formulation of goserelin acetate administered every 13 weeks to patients with advanced prostate cancer. *Br J Urol Int* 1999;83(7):801-6.

Sharifi R, Soloway M, the Leuprolide Study Group.

Clinical study of leuprolide depot formulation in the treatment of advanced prostate cancer. *J Urol* 1990;143(1):68-71.

Turkes AO, Peeling WB, Griffiths K.

Treatment of patients with advanced cancer of the prostate: phase III trial, Zoladex against castration; a study of the British Prostate Group. *J Steroid Biochem* 1987;27(1-3):543-9.

Turkes A, Turkes A, Peeling B, Griffiths K.

The use of a depot LHRH analogue, Zoladex, in the treatment of prostatic cancer: a dose-interval study. *Med Sci Res* 1987;15:477.

Van Cangh PJ, Opsomer RJ.

Treatment of advanced carcinoma of the prostate with a depot luteinizing hormone-releasing hormone analogue (ICI-118630). *J Urol* 1987;137(1):61-4.

Visscher GE, Robison RL, Maulding HV, Fong JW, Pearson JE, Argentieri GJ.

Biodegradation of and tissue reaction to 50:50 poly(DL-lactide-co-glycolide) microcapsules. *J Biomed Mater Res* 1985;19:349-65.

Walker KJ, Turkes AO, Turkes A, Zwink R, Beacock C, Buck AC, et al.

Treatment of patients with advanced cancer of the prostate using a slow-release (depot) formulation of the LHRH agonist ICI 118630 (Zoladex). *J Endocrinol* 1984;103(2):R1-4.

Waxman J.

Analogues of gonadotrophin releasing hormone. *Br Med J Clin Res Ed* 1984;288(6415):426-7.

Waymont B, Lynch TH, Dunn JA, Emtage LA, Arkell DG, Wallace DM, et al.

Phase III randomised study of Zoladex versus stilboestrol in the treatment of advanced prostate cancer. *Br J Urol* 1992;69(6):614-20.

Williams G.

Endocrine treatment of prostatic cancer. *J R Soc Med* 1985;78(10):797-9.

Williams G, Bloom SR.
Treatment of advanced carcinoma of the prostate. Br Med J Clin Res Ed
1984;289(6445):571-2.

Williams G, Kerle D, Griffin S, Dunlop H, Bloom SR.
Biodegradable polymer luteinising hormone releasing hormone analogue for prostatic cancer:
use of a new peptide delivery system. Br Med J Clin Res Ed 1984;289(6458):1580-1.

**PART III:
CONSUMER INFORMATION**

Pr
Zoladex[®] LA
goserelin depot

This leaflet is part III of a three-part "Product Monograph" published when ZOLADEX[®] LA 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 LA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What ZOLADEX LA is used for:

Prostate Cancer

ZOLADEX LA 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).

Benign Conditions

ZOLADEX LA 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.

What ZOLADEX LA does:

ZOLADEX LA treatment, given as recommended, results in suppression of your sex hormones (testosterone in men and estradiol in women). Any complaints you experience may be related to this hormone-suppressing action of ZOLADEX LA. These complaints may include hot flushes, swollen or tender breasts and reduction in sex drive.

When ZOLADEX LA should not be used:

You should not use ZOLADEX LA if:

- You are allergic to goserelin acetate or any nonmedicinal ingredients in ZOLADEX LA.
- 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 LA comes in:

ZOLADEX LA comes in a hard, cream-coloured, rod-shaped depot which contains 10.8mg of goserelin as goserelin acetate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

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

ZOLADEX LA 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 LA. 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 LA.

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

ZOLADEX LA is not recommended for use in children.

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

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

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

- Have or have had any problem 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 LA may increase the risk of having an abnormal heart rhythm (QT prolongation).
- Have diabetes.
- Are pregnant or planning to become pregnant. ZOLADEX LA 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 LA. After stopping ZOLADEX LA it may take longer for some women to experience menses. Rarely, some women may enter menopause. If 12 weeks have passed after the last ZOLADEX LA injection and you do not experience menses, talk to your doctor.
- Taking blood thinners.

INTERACTIONS WITH THIS MEDICATION

Check with your doctor or pharmacist before taking any other drugs, including non-prescription drugs (for colds, nausea, etc.). ZOLADEX LA 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 LA is given as an injection under the skin of the abdomen by a trained health care professional, such as a doctor or nurse.
- **Prostate cancer:** one injection every 3 months
- **Endometriosis:** one injection every 12 weeks
- 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 LA.

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 LA. 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.

Use of ZOLADEX LA In Men

- When you first start receiving ZOLADEX LA 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 LA in Women

- For pre-menopausal women: menstruation stops with the 12 week depot of ZOLADEX LA. If regular menstruation persists, notify your doctor. Occasionally some women may enter menopause early, so when ZOLADEX LA treatment is stopped menstruation will not start again.

- 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.
- ZOLADEX LA has been associated with the formation of ovarian cysts, which may cause pain for some women.

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 LA 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		√	
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 LA IN WOMEN			
Very Common (more than 10 in every 100 patients are likely to have them)			
Reduced sex drive	√		
Hot flushes and sweating	√		

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	
Acne*	√		
Vaginal dryness	√		
Change in breast size	√		
Injection site reaction	√		
Common (1 to 10 in every 100 patients are likely to have them)			
Mood changes including depression		√	
Tingling in fingers and toes	√		
Headache		√	
Changes in blood pressure		√	
Skin rashes	√		
Thinning of bones		√	
Joint pain		√	
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 LA.

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

HOW TO STORE IT

- ZOLADEX LA should not be used after the expiry date on the pack. Store ZOLADEX LA in its original pack between 2°C and 25°C.
- If your doctor decides to stop your treatment, return ZOLADEX LA to the pharmacy for proper disposal
- Keep your ZOLADEX LA 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

This leaflet was prepared by:

TerSera Therapeutics LLC Lake Forest, IL 60045

ZOLADEX® and SAFESYSTEM® are registered trademarks of AstraZeneca or its affiliates and are used herein under license.

©2017 TerSera Therapeutics LLC

Last revised: December 21, 2017