

NDA 019726/S-054

Zoladex (goserelin acetate
implant) 3.6 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOLADEX safely and effectively. See full prescribing information for ZOLADEX.

ZOLADEX® (goserelin acetate implant) 3.6 mg

Initial U.S. Approval: 1989

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions, Hyperglycemia and Diabetes (5.3), 12/2010
Warnings and Precautions, Cardiovascular Diseases (5.4), 12/2010

-----**INDICATIONS AND USAGE**-----

ZOLADEX is a Gonadotropin Releasing Hormone (GnRH) agonist indicated for:

- Use in combination with flutamide for the management of locally confined carcinoma of the prostate (1.1)
- Palliative treatment of advanced carcinoma of the prostate (1.2)
- The management of endometriosis (1.3)
- Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (1.4)
- Use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women (1.5)

-----**DOSAGE AND ADMINISTRATION**-----

- ZOLADEX 3.6 mg should be administered subcutaneously every 28 days (2.1- 2.7)
- For the management of endometriosis, the recommended duration of administration is 6 months for women 18 years of age and older (2.3)

-----**DOSAGE FORMS AND STRENGTHS**-----

Implant 3.6 mg (3)

-----**CONTRAINDICATIONS**-----

- Hypersensitivity (4.1)
- Pregnancy unless used for treatment of advanced breast cancer (4.2)

-----**WARNINGS AND PRECAUTIONS**-----

- Women of Childbearing Potential and Pregnancy: Pregnancy must be excluded for use in benign gynecological conditions. Women should avoid pregnancy. (5.1)
- Tumor Flare Phenomenon: Transient worsening of tumor symptoms may occur during the first few weeks of treatment with ZOLADEX, which may include ureteral obstruction and spinal cord compression. Monitor patients at risk for complications of tumor flare. (5.2 and 6.2)

- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (5.3)
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice. (5.4)
- Hypercalcemia: Hypercalcemia has been reported in patients with bone metastases treated with ZOLADEX. Monitor and manage appropriately. (5.4)
- Hypersensitivity: Systemic hypersensitivity has been reported in patients receiving goserelin/ZOLADEX implants. (4.1, 5.5 and 6.10)
- Cervical Resistance: Increase in cervical resistance may occur. Caution is recommended when dilating the cervix for endometrial ablation. (5.6)

-----**ADVERSE REACTIONS**-----

The most common, clinically significant adverse reactions occurring in >10% of men: hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms (6)

The adverse event profile was similar for women treated for breast cancer, dysfunctional uterine bleeding or endometriosis and included (>20%): hot flashes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea, and peripheral edema (6)

Tumor flare can occur on the initiation of ZOLADEX for both men and women being treated for cancer (6)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

-----**DRUG INTERACTIONS**-----

- None

-----**USE IN SPECIFIC POPULATIONS**-----

- Nursing mothers: Discontinue drug or nursing taking into account the importance of drug to the mother (8.3)
- No information available for use in Pediatric Patients (8.4)
- Geriatric (8.5)
- Renal and Hepatic Impairment: No dose adjustment is necessary (2.6, 8.6 and 8.7)

-----**SEE 17 FOR PATIENT COUNSELING INFORMATION**-----

Revised 12/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Stage B2-C Prostatic Carcinoma

ZOLADEX is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with ZOLADEX and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy [see *Dosage and Administration (2.1) and Clinical Studies (14.1)*].

1.2 Prostatic Carcinoma

ZOLADEX is indicated in the palliative treatment of advanced carcinoma of the prostate [see *Dosage and Administration (2.2) and Clinical Studies (14.2)*].

1.3 Endometriosis

ZOLADEX is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with ZOLADEX for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months [see *Dosage and Administration (2.3) and Clinical Studies (14.3)*].

1.4 Endometrial Thinning

ZOLADEX is indicated for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding [see *Dosage and Administration (2.4) and Clinical Studies (14.4)*].

1.5 Advanced Breast Cancer

ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.

The estrogen and progesterone receptor values may help to predict whether ZOLADEX therapy is likely to be beneficial [see *Dosage and Administration (2.6), Clinical Pharmacology (12.1), and Clinical Studies (14.5)*].

The automatic safety feature of the syringe aids in the prevention of needlestick injury.

2 DOSAGE AND ADMINISTRATION

ZOLADEX, at a dose of 3.6 mg, should be administered subcutaneously every 28 days into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician [see *Dosage and Administration (2.7)*].

While a delay of a few days is permissible, every effort should be made to adhere to the 28-day schedule.

2.1 Stage B2-C Prostatic Carcinoma

When ZOLADEX is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using a ZOLADEX 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the ZOLADEX 10.8 mg depot, can be administered. Alternatively, four injections of 3.6 mg depot can be administered at 28-day intervals, two depots preceding and two during radiotherapy.

2.2 Prostatic Carcinoma

For the management of advanced prostate cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

2.3 Endometriosis

For the management of endometriosis, the recommended duration of administration is 6 months.

Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months.

Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with ZOLADEX is contemplated, consideration should be given to monitoring bone mineral density. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The addition of Hormone Replacement Therapy may also reduce the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism. The optimal drugs, dose and duration of treatment has not been established.

2.4 Endometrial Thinning

For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is one or two depots (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two depots are administered, surgery should be performed within two to four weeks following administration of the second depot.

2.5 Breast Cancer

For the management of advanced breast cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

2.6 Renal or Hepatic Impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment.

2.7 Administration Technique

The proper method of administration of ZOLADEX is described in the instructions that follow.

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.
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 implant is visible.

3. Grasp the red plastic safety tab and pull away from the syringe, and discard. Remove needle cover. **Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the ZOLADEX implant.**
4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the skin of the patient's anterior abdominal wall below the navel line. With the bevel of the needle facing up, **insert the needle at a 30 to 45 degree angle to the skin** in one continuous deliberate motion until the protective sleeve touches the patient's skin.
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 inject with a new syringe elsewhere.
5. Do not penetrate into muscle or peritoneum.
6. To administer the ZOLADEX implant and to activate the protective sleeve, grasp the barrel at the finger grip and depress the plunger until you cannot depress it any further. If the plunger is not depressed **fully**, the protective sleeve will **NOT** activate. When the protective sleeve 'clicks', the protective sleeve will automatically begin to slide to cover the needle.
NOTE: The needle does not retract.
7. Withdraw the needle and allow protective sleeve 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 ZOLADEX, it may be localized by ultrasound.

3 DOSAGE FORMS AND STRENGTHS

ZOLADEX is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem™ Syringe] (NDC 0310-0950-36).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Anaphylactic reactions to ZOLADEX have been reported in the medical literature. ZOLADEX is contraindicated in those patients who have a known hypersensitivity to GnRH, GnRH agonist analogues or any of the components in ZOLADEX.

4.2 Pregnancy

ZOLADEX is contraindicated during pregnancy unless ZOLADEX is being used for palliative treatment of advanced breast cancer. ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. There is an increased risk for pregnancy loss due to expected hormone changes that occur with ZOLADEX treatment [*see Use in Specific Populations (8.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Women of Childbearing Potential and Pregnancy

Before starting treatment with ZOLADEX, pregnancy must be excluded for women using ZOLADEX for benign gynecological conditions. Women of childbearing potential should be advised to avoid becoming pregnant.

Effective nonhormonal contraception must be used by all premenopausal women during ZOLADEX therapy and for 12 weeks following discontinuation of therapy. When used every 28 days, ZOLADEX usually inhibits ovulation and stops menstruation; however, pregnancy prevention is not ensured. Effects on reproductive function are expected to occur with chronic administration as a result of the anti-gonadotrophic properties of the drug.

Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies, ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy for the palliative treatment of breast cancer, then the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

5.2 Tumor Flare Phenomenon

Initially, ZOLADEX, like other GnRH agonists, causes transient increases in serum levels of testosterone in men with prostate cancer, and estrogen in women with breast cancer. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate or breast cancer, may occasionally develop during the first few weeks of ZOLADEX treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

As with other GnRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed in patients with prostate cancer. If spinal cord compression or renal impairment secondary to ureteral obstruction develops, standard treatment of these complications should be instituted. For extreme cases in prostate cancer patients, an immediate orchiectomy should be considered.

5.3 Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes [*see Adverse Reactions (6.10) and Patient Counseling Information (17.1)*].

5.4 Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice [*see Patient Counseling Information (17.1)*].

5.5 Hypercalcemia

As with other GnRH agonists or hormonal therapies (antiestrogens, estrogens, etc.), hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after starting treatment with ZOLADEX. If hypercalcemia does occur, appropriate treatment measures should be initiated.

5.6 Hypersensitivity

Hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with GnRH agonist analogues [see Contraindications (4.1) and Adverse Reactions (6.10)].

Of 115 women worldwide treated with ZOLADEX and tested for development of binding to goserelin following treatment with ZOLADEX, one patient showed low-titer binding to goserelin. On further testing of this patient's plasma obtained following treatment, her goserelin binding component was found not to be precipitated with rabbit antihuman immunoglobulin polyvalent sera. These findings suggest the possibility of antibody formation.

5.7 Cervical Resistance

The pharmacologic action of ZOLADEX on the uterus and cervix may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix for endometrial ablation.

6 ADVERSE REACTIONS

6.1 Stage B2-C Prostatic Carcinoma

Treatment with ZOLADEX and flutamide did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing ZOLADEX + flutamide + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below:

Table 1 ADVERSE EVENTS DURING ACUTE RADIATION THERAPY (within first 90 days of radiation therapy)

	(n=231) flutamide + ZOLADEX + Radiation	(n = 235) Radiation Only
	% All	% All
Rectum/Large Bowel	80	76
Bladder	58	60
Skin	37	37

Table 2 ADVERSE EVENTS DURING LATE RADIATION PHASE (after 90 days of radiation therapy)

	(n=231) flutamide + ZOLADEX + Radiation	(n = 235) Radiation Only
	% All	% All
Diarrhea	36	40
Cystitis	16	16
Rectal Bleeding	14	20
Proctitis	8	8

	(n=231)	(n = 235)
	flutamide + ZOLADEX + Radiation	Radiation Only
	% All	% All
Hematuria	7	12

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

6.2 Prostatic Carcinoma

ZOLADEX has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients' withdrawal from ZOLADEX treatment. As seen with other hormonal therapies, the most commonly observed adverse events during ZOLADEX therapy were due to the expected physiological effects from decreased testosterone levels. These included hot flashes, sexual dysfunction and decreased erections.

Tumor Flare Phenomenon: Initially, ZOLADEX, like other GnRH agonists, causes transient increases in serum levels of testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms, usually manifested by an increase in cancer-related pain which was managed symptomatically. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both ZOLADEX and orchiectomy. The relationship of these events to therapy is uncertain [see *Warnings and Precautions (5.2)*].

In the controlled clinical trials of ZOLADEX versus orchiectomy, the following events were reported as adverse reactions in greater than 5% of the patients.

Table 3 TREATMENT RECEIVED

ADVERSE EVENT	ZOLADEX	ORCHIECTOMY
	(n=242) %	(n=254) %
Hot Flashes	62	53
Sexual Dysfunction	21	15
Decreased Erections	18	16
Lower Urinary Tract Symptoms	13	8
Lethargy	8	4
Pain (worsened in the first 30 days)	8	3
Edema	7	8
Upper Respiratory Infection	7	2
Rash	6	1
Sweating	6	4
Anorexia	5	2
Chronic Obstructive Pulmonary Disease	5	3
Congestive Heart Failure	5	1
Dizziness	5	4

ADVERSE EVENT	ZOLADEX	ORCHIECTOMY
	(n=242) %	(n=254) %
Insomnia	5	1
Nausea	5	2
Complications of Surgery	0	18†

† Complications related to surgery were reported in 18% of the orchiectomy patients, while only 3% of ZOLADEX patients reported adverse reactions at the injection site. The surgical complications included scrotal infection (5.9%), groin pain (4.7%), wound seepage (3.1%), scrotal hematoma (2.8%), incisional discomfort (1.6%) and skin necrosis (1.2%).

The following additional adverse reactions were reported in greater than 1% but less than 5% of the patients treated with ZOLADEX: **CARDIOVASCULAR** - arrhythmia, cerebrovascular accident, hypertension, myocardial infarction, peripheral vascular disorder, chest pain; **CENTRAL NERVOUS SYSTEM** - anxiety, depression, headache; **GASTROINTESTINAL** - constipation, diarrhea, ulcer, vomiting; **HEMATOLOGIC** - anemia; **METABOLIC/NUTRITIONAL** - gout, hyperglycemia, weight increase; **MISCELLANEOUS** - chills, fever; **UROGENITAL** - renal insufficiency, urinary obstruction, urinary tract infection, breast swelling and tenderness.

6.3 Females

As would be expected with a drug that results in hypoestrogenism, the most frequently reported adverse reactions were those related to this effect.

6.4 Endometriosis

In controlled clinical trials comparing ZOLADEX every 28 days and danazol daily for the treatment of endometriosis, the following events were reported at a frequency of 5% or greater:

Table 4 TREATMENT RECEIVED

ADVERSE EVENT	ZOLADEX	DANAZOL
	(n=411) %	(n=207) %
Hot Flushes	96	67
Vaginitis	75	43
Headache	75	63
Emotional Lability	60	56
Libido Decreased	61	44
Sweating	45	30
Depression	54	48
Acne	42	55
Breast Atrophy	33	42
Seborrhea	26	52
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

ADVERSE EVENT	ZOLADEX (n=411) %	DANAZOL (n=207) %
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
Pruritus	2	6
Hypertonia	1	10

The following adverse events not already listed above were reported at a frequency of 1% or greater, regardless of causality, in ZOLADEX-treated women from all clinical trials: **WHOLE BODY** - allergic reaction, chest pain, fever, malaise; **CARDIOVASCULAR** - hemorrhage, hypertension, migraine, palpitations, tachycardia; **DIGESTIVE** - anorexia, constipation, diarrhea, dry mouth, dyspepsia, flatulence; **HEMATOLOGIC** - ecchymosis; **METABOLIC AND NUTRITIONAL** - edema; **MUSCULOSKELETAL** - arthralgia, joint disorder; **CNS** - anxiety, paresthesia, somnolence, thinking abnormal; **RESPIRATORY** - bronchitis, cough increased, epistaxis, rhinitis, sinusitis; **SKIN** - alopecia, dry skin, rash, skin discoloration; **SPECIAL SENSES** - amblyopia, dry eyes; **UROGENITAL** - dysmenorrhea, urinary frequency, urinary tract infection, vaginal hemorrhage.

6.5 Endometrial Thinning

The following adverse events were reported at a frequency of 5% or greater in premenopausal women presenting with dysfunctional uterine bleeding in Trial 0022 for endometrial thinning. These results indicate that headache, hot flushes and sweating were more common in the ZOLADEX group than in the placebo group.

Table 5 ADVERSE EVENTS REPORTED AT A FREQUENCY OF 5% OR GREATER IN ZOLADEX AND PLACEBO TREATMENT GROUPS OF TRIAL 0022

ADVERSE EVENT	ZOLADEX 3.6 mg (n=180) %	Placebo (n=177) %
Whole Body		
Headache	32	22
Abdominal Pain	11	10
Pelvic Pain	9	6

ADVERSE EVENT	ZOLADEX 3.6 mg (n=180) %	Placebo (n=177) %
Back Pain	4	7
Cardiovascular		
Vasodilatation	57	18
Migraine	7	4
Hypertension	6	2
Digestive		
Nausea	5	6
Nervous		
Nervousness	5	3
Depression	3	7
Respiratory		
Pharyngitis	6	9
Sinusitis	3	6
Skin and appendages		
Sweating	16	5
Urogenital		
Dysmenorrhea	7	9
Uterine Hemorrhage	6	4
Vulvovaginitis	5	1
Menorrhagia	4	5
Vaginitis	1	6

6.6 Breast Cancer

The adverse event profile for women with advanced breast cancer treated with ZOLADEX is consistent with the profile described above for women treated with ZOLADEX for endometriosis. 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.

ADVERSE EVENT	TREATMENT RECEIVED	
	ZOLADEX (n=57) % of Pts.	OOPHORECTOMY (n=55) % of Pts.
Hot Flashes	70	47
Tumor 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 flashes were reported in 75.9% of patients and decreased libido was noted in 47.7% of patients. These two adverse events reflect the pharmacological actions of ZOLADEX.

Injection site reactions were reported in less than 1% of patients.

6.7 Hormone Replacement Therapy

Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.

6.8 Changes in Bone Mineral Density

After 6 months of ZOLADEX treatment, 109 female patients treated with ZOLADEX showed an average 4.3% 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. Sixty-six of these patients were assessed for BMD loss 6 months after the completion (posttherapy) of the 6-month therapy period. Data from these patients showed an average 2.4% BMD loss compared to pretreatment values. Twenty-eight of the 109 patients were assessed for BMD at 12 months posttherapy. 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. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The optimal drugs, dose and duration of treatment has not been established [*see Patient Counseling Information (17.2)*].

6.9 Changes in Laboratory Values During Treatment

Plasma Enzymes: Elevation of liver enzymes (AST, ALT) have been reported in female patients exposed to ZOLADEX (representing less than 1% of all patients).

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, danazol treatment resulted in a mean increase in LDL cholesterol of 33.3 mg/dL and a decrease in HDL cholesterol of 21.3 mg/dL compared to increases of 21.3 and 2.7 mg/dL in LDL cholesterol and HDL cholesterol, respectively, for ZOLADEX-treated patients. Triglycerides increased by 8.0 mg/dL in ZOLADEX-treated patients compared to a decrease of 8.9 mg/dL in danazol-treated patients.

In patients treated for endometriosis, ZOLADEX increased total cholesterol and LDL cholesterol during 6 months of treatment. However, ZOLADEX therapy resulted in HDL cholesterol levels which were significantly higher relative to danazol therapy. At the end of 6 months of treatment, HDL cholesterol fractions (HDL₂ and HDL₃) were decreased by 13.5 and 7.7 mg/dL, respectively, for danazol-treated patients compared to treatment increases of 1.9 and 0.8 mg/dL, respectively, for ZOLADEX-treated patients.

6.10 Post-Marketing

Hypersensitivity: Rarely, hypersensitivity reactions (including urticaria and anaphylaxis) have been reported in patients receiving ZOLADEX [*see Contraindications (4.1) and Warnings and Precautions (5.5)*].

Bone Mineral Density: There have been post-marketing reports of osteoporosis, decreased bone mineral density and bony fracture in men treated with ZOLADEX for prostate cancer [see *Patient Counseling Information (17.1) and (17.2)*].

Cardiovascular: Cases of serious venous and arterial thromboembolism have been reported in women receiving GnRH agonists, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

Ovarian Cyst: As with other GnRH agonists, there have been reports of ovarian cyst formation and, when ZOLADEX 3.6 mg is used in combination with gonadotropins, of ovarian hyperstimulation syndrome (OHSS).

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

Pituitary Apoplexy and Tumors: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed. Most of the pituitary apoplexy cases occurred within 2 weeks of the first dose, and some occurred within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required. Very rare cases of pituitary tumors have been reported.

Glucose Tolerance: Reduction in glucose tolerance, manifesting as diabetes or loss of glycemic control in those with pre-existing diabetes, has been reported during treatment with GnRH agonists, including ZOLADEX [see *Warnings and Precautions (5.3) and Patient Counseling Information (17.1)*].

Other Adverse Reactions: Psychotic disorders have also been reported.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed. No confirmed interactions have been reported between ZOLADEX and other drugs.

7.1 Drug/Laboratory Test Interactions

Administration of ZOLADEX in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment and until the resumption of menses may show results which are misleading. Normal function is usually restored within 12 weeks after treatment is discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D in patients with advanced breast cancer.

Pregnancy Category X in patients with endometriosis and endometrial thinning.

ZOLADEX is contraindicated during pregnancy unless ZOLADEX is being used for palliative treatment of advanced breast cancer. There are no adequate and well-controlled studies in pregnant women using ZOLADEX. Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies, ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. There is an increased risk for pregnancy loss due to expected hormone changes that occur with ZOLADEX treatment.

ZOLADEX crosses the placenta in rats and rabbits following subcutaneous administration. Administration of goserelin to pregnant rats and rabbits during organogenesis resulted in increased preimplantation loss and increased resorptions. When pregnant rats received goserelin throughout gestation and lactation, there was a dose-related increase in umbilical hernia in offspring. In additional reproduction studies in rats, goserelin decreased fetus and pup survival. Human dose/exposure multiples could not be calculated from available animal data.

Actual animal doses: rat (≥ 2 mcg/kg/day for pregnancy loss; ≥ 10 mcg/kg/day for umbilical hernia in offspring); rabbits (> 20 mcg/kg/day).

8.3 Nursing Mothers

It is not known if goserelin is excreted in human milk. Goserelin is excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZOLADEX, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There is no need for any dosage adjustment when administering ZOLADEX to male geriatric patients. ZOLADEX has not been studied in women over 65 years.

8.6 Renal Insufficiency

In clinical trials with the solution formulation of goserelin, male patients with impaired renal function (creatinine clearance < 20 mL/min) had a total body clearance and serum elimination half-life of 31.5 mL/min and 12.1 hours, respectively, compared to 133 mL/min and 4.2 hours for subjects with normal renal function (creatinine clearance > 70 mL/min). In females, the effects of reduced goserelin clearance due to impaired renal function on drug efficacy and toxicity are unknown. Pharmacokinetic studies in patients with renal impairment do not indicate a need for dose adjustment with the use of the depot formulation.

8.7 Hepatic Insufficiency

The total body clearances and serum elimination half-lives were similar between normal subjects and patients with moderate hepatic impairment (alanine transaminase < 3 xULN and aspartate aminotransferase < 3 xULN) when treated with a 250 mcg subcutaneous formulation of goserelin. This pharmacokinetic study indicates that no dose adjustment is needed in patients with moderately impaired liver function. There is no pharmacokinetic data with goserelin in patients with severe hepatic insufficiency.

10 OVERDOSAGE

The pharmacologic properties of ZOLADEX and its mode of administration make accidental or intentional overdosage unlikely. There is no experience of overdosage from clinical trials. Animal studies indicate that no increased pharmacologic effect occurred at higher doses or more frequent administration. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs did not produce any nonendocrine related sequelae; this dose is up to 250 times the estimated human daily dose based on the body surface area. If overdosage occurs, it should be managed symptomatically.

11 DESCRIPTION

ZOLADEX® (goserelin acetate implant) is a GnRH agonist. Goserelin acetate is chemically described as an acetate salt of [D-Ser(Bu¹)⁶,Azgly¹⁰]. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu¹)-Leu-Arg-Pro-Azgly-NH₂ acetate [C₅₉H₈₄N₁₈O₁₄ ·(C₂H₄O₂)_x where x = 1 to 2.4].

Goserelin acetate is an off-white powder with a molecular weight of 1269 Daltons (free base). It is freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform and ether.

ZOLADEX is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. ZOLADEX is designed for subcutaneous injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white to cream colored 1-mm diameter cylinder, preloaded in a special single use syringe with a 16-gauge x 36 +/- 0.5 mm siliconized needle with protective needle sleeve (SafeSystem™ Syringe) in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZOLADEX is a synthetic decapeptide analogue of GnRH. ZOLADEX acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. In animal and *in vitro* studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor.

12.2 Pharmacodynamics

Following initial administration in males, ZOLADEX causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of ZOLADEX leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy. This leads to accessory sex organ regression. In clinical trials with follow-up of more than 2 years, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to ZOLADEX leads to suppression of gonadotropin secretion, a decrease in serum estradiol to levels consistent with the postmenopausal state, and would be expected to lead to a reduction of ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone-responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the patients enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within four weeks after initial administration of drug and are usually maintained at that range with continued use of ZOLADEX. In 5% or less of women treated with ZOLADEX, FSH and LH levels may not be suppressed to follicular phase levels on day 28 post treatment with use of a single 3.6 mg depot injection. In certain individuals, suppression of any of these hormones to such levels may not be achieved with ZOLADEX. Estradiol, LH and FSH levels return to pretreatment values within 12 weeks following the last implant administration in all but rare cases.

12.3. Pharmacokinetics

The pharmacokinetics of ZOLADEX have been determined in both male and female healthy volunteers and patients. In these studies, ZOLADEX was administered as a single 250 mcg (aqueous solution) dose and as a single or multiple 3.6 mg depot dose by subcutaneous route.

Absorption

The absorption of radiolabeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing. The mean (\pm standard deviation) pharmacokinetic parameter estimates of ZOLADEX after administration of 3.6 mg depot for 2 months in males and females are presented in the following table.

Table 7 – Pharmacokinetic Parameter Estimates

Parameter (units)	Males n=7	Females n=9
Peak Plasma Concentration (ng/mL)	2.84 \pm 1.81	1.46 \pm 0.82
Time to Peak Concentration (days)	12-15	8-22
Area Under the Curve (0-28 days) (ng.d/mL)	27.8 \pm 15.3	18.5 \pm 10.3
Systemic Clearance (mL/min)	110.5 \pm 47.5	163.9 \pm 71.0

Goserelin is released from the depot at a much slower rate initially for the first 8 days, and then there is more rapid and continuous release for the remainder of the 28-day dosing period. Despite the change in the releasing rate of goserelin, administration of ZOLADEX every 28 days resulted in testosterone levels that were suppressed to and maintained in the range normally seen in surgically castrated men.

When ZOLADEX 3.6 mg depot was used for treating male and female patients with normal renal and hepatic function, there was no significant evidence of drug accumulation. However, in clinical trials the minimum serum levels of a few patients were increased. These levels can be attributed to interpatient variation.

Distribution

The apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. The plasma protein binding of goserelin obtained from one sample was found to be 27.3%.

Metabolism

Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component presented in urine of one healthy male volunteer was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion

Clearance of goserelin following subcutaneous administration of the solution formulation of goserelin is very rapid and occurs via a combination of hepatic metabolism and urinary excretion. More than 90% of a subcutaneous radiolabeled solution formulation dose of goserelin is excreted in urine. Approximately 20% of the dose in urine is accounted for by unchanged goserelin. The total body clearance of goserelin (administered subcutaneously as a 3.6 mg depot) was significantly ($p < 0.05$) greater (163.9 versus 110.5 L/min) in females compared to males.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Subcutaneous implantation of goserelin in male and female rats once every 4 weeks for 1 year and recovery for 23 weeks at doses of about 80 and 150 mcg/kg (males) and 50 and 100 mcg/kg (females) daily resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following subcutaneous implant of goserelin in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females. The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of goserelin every 3 weeks for 2 years delivered to mice at doses of up to 2400 mcg/kg/day resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur. Human dose/exposure multiples could not be calculated from available animal data.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 mcg/kg/day, a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 mcg/kg/day, suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the testes, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs were reversible in male and female dogs administered 107-214 mcg/kg/day goserelin when drug treatment was stopped after continuous administration for 1 year. Human dose/exposure multiples could not be calculated from available animal data.

14 CLINICAL STUDIES

14.1 Stage B2-C Prostatic Carcinoma

The effects of hormonal treatment combined with radiation were studied in 466 patients (231 ZOLADEX + flutamide + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of ZOLADEX (3.6 mg depot) and flutamide capsules (250 mg t.i.d.) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years, $P < 0.001$). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, $P = 0.058$). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, $P < 0.001$). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, $P < 0.001$).

14.2 Prostatic Carcinoma

In controlled studies of patients with advanced prostatic cancer comparing ZOLADEX to orchiectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the two treatment arms in a comparative trial.

14.3 Endometriosis

In controlled clinical studies using the 3.6 mg formulation every 28 days for 6 months, ZOLADEX was shown to be as effective as danazol therapy in relieving clinical symptoms (dysmenorrhea, dyspareunia and pelvic pain) and signs (pelvic tenderness, pelvic induration) of endometriosis and decreasing the size of endometrial lesions as determined by laparoscopy. In one study comparing ZOLADEX with danazol (800 mg/day), 63% of ZOLADEX-treated patients and 42% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. In the second study comparing ZOLADEX with danazol (600 mg/day), 62% of ZOLADEX-treated and 51% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. The clinical significance of a decrease in endometriotic lesions is not known at this time; and in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In these two studies, ZOLADEX led to amenorrhea in 92% and 80%, respectively, of all treated women within 8 weeks after initial administration. Menses usually resumed within 8 weeks following completion of therapy.

Within 4 weeks following initial administration, clinical symptoms were significantly reduced, and at the end of treatment were, on average, reduced by approximately 84%.

During the first two months of ZOLADEX use, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding, and is expected to stop spontaneously.

There is insufficient evidence to determine whether pregnancy rates are enhanced or adversely affected by the use of ZOLADEX.

14.4 Endometrial Thinning

Two trials were conducted with ZOLADEX prior to endometrial ablation for dysfunctional uterine bleeding.

Trial 0022, was a double-blind, prospective, randomized, parallel-group multicenter trial conducted in 358 premenopausal women with dysfunctional uterine bleeding. Eligible patients were randomized to receive either two depots of ZOLADEX 3.6 mg (n=180) or two placebo injections (n=178) administered four weeks apart. 175 patients in each group underwent endometrial ablation using either diathermy loop alone or in combination with rollerball approximately 2 weeks after the second injection. Endometrial thickness was assessed immediately before surgery using a transvaginal ultrasonic probe. The incidence of amenorrhea was compared between the ZOLADEX and placebo groups at 24 weeks after endometrial ablation.

The median endometrial thickness before surgery was significantly less in the ZOLADEX treatment group (1.50 mm) compared to the placebo group (3.55 mm). Six months after surgery, 40% of patients (70/175) treated with ZOLADEX in Trial 0022 reported amenorrhea as compared with 26% who had received placebo injections (44/171), a difference that was statistically significant.

Trial 0003, was a single center, open-label, randomized trial in premenopausal women with dysfunctional uterine bleeding. The trial allowed for a comparison of 1 depot of ZOLADEX and 2 depots of ZOLADEX administered 4 weeks apart with ablation using Nd: YAG laser occurring 4 weeks after ZOLADEX administration. Forty patients were randomized into each of the ZOLADEX treatment groups.

The median endometrial thickness before surgery was significantly less in the group treated with two depots (0.5 mm) compared to the group treated with one depot (1 mm). No difference in the incidence of amenorrhea was found at 24 weeks (24% in both groups). Of the 74 patients that completed the trial, 53% reported hypomenorrhea and 20% reported normal menses six months after surgery.

14.5 Breast Cancer

The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG-8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared ZOLADEX with oophorectomy. On the basis of interim data from 124 women, the best objective response (CR+PR) for the ZOLADEX group is 22% versus 12% for the oophorectomy group. The median time to treatment failure is 6.7 months for patients treated with ZOLADEX and 5.5 months for patients treated with oophorectomy. The median survival time for the ZOLADEX arm is 33.2 months and for the oophorectomy arm is 33.6 months.

Subjective responses based on measures of pain control and performance status were observed with both treatments; 48% of the women in the ZOLADEX treatment group and 50% in the oophorectomy group had subjective responses. In the clinical trial (SWOG-8692 [INT-0075]), the mean post treatment estradiol level was reported as 17.8 pg/mL. (The mean estradiol level in post-menopausal women as reported in the literature is 13 pg/mL). During the conduct of the clinical trial, women whose estradiol levels were not reduced to the postmenopausal range, received two ZOLADEX depots, thus, increasing the dose of ZOLADEX from 3.6 mg to 7.2 mg.

Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancer. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2302) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in the following table.

Table 10 OBJECTIVE RESPONSE BY ER STATUS

ER Status	CR + PR/Total No.	
	(%)	
	Phase II (N=228)	Trial 2302 (N=159)
Positive	43/119 (36)	31/86 (36)
Negative	6/33 (18)	3/26 (10)
Unknown	20/76 (26)	18/44 (41)

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOLADEX is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem™ Syringe] (NDC 0310-0950-36). The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C [77°F]).

17 PATIENT COUNSELING INFORMATION

17.1 Males

The use of ZOLADEX in patients at particular risk of developing ureteral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. Patients with ureteral obstruction or spinal cord compression should have appropriate treatment prior to initiation of ZOLADEX therapy [*see Warnings and Precautions (5.2) and Adverse Reactions (6.2)*].

The use of GnRH agonists may cause a reduction in bone mineral density. In men, data suggest the use of a bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss [*see Adverse Reactions (6.8) and (6.10)*].

Patients should be informed that diabetes or loss of glycemic control in patients with pre-existing diabetes has been reported during treatment with GnRH agonists, including ZOLADEX. Therefore, consideration should be given to monitoring blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving ZOLADEX [*see Warnings and Precautions (5.3) and Adverse Reactions (6.10)*].

A small increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice [*see Warnings and Precautions (5.4)*].

17.2 Females

1. Menstruation should stop with effective doses of ZOLADEX. The patient should notify her physician if regular menstruation persists. Patients missing one or more successive doses of ZOLADEX may experience breakthrough menstrual bleeding [*see Warnings and Precautions (5.1)*].
2. ZOLADEX should not be used in a pregnant or breastfeeding woman except for the palliative treatment of advanced breast cancer. ZOLADEX may harm the fetus and increase the risk for pregnancy loss [*see Contraindications (4.2), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].
3. A woman should not begin ZOLADEX treatment if she has undiagnosed abnormal vaginal bleeding, or is allergic to any of the components of ZOLADEX [*see Clinical Studies (14.3)*].
4. Premenopausal women using ZOLADEX must use nonhormonal contraception during treatment and for 12 weeks after treatment ends [*see Warnings and Precautions (5.1)*].

5. If a patient becomes pregnant while using ZOLADEX for endometriosis or endometrial thinning, ZOLADEX treatment should be discontinued. The patient should be advised of the possible risks to the pregnancy and fetus, including an increased risk of pregnancy loss [*see Contraindications (4.2) and Use In Specific Populations (8.1)*].
6. Those adverse events occurring most frequently in clinical studies with ZOLADEX are associated with hypoestrogenism; of these, the most frequently reported are hot flashes (flushes), headaches, vaginal dryness, emotional lability, change in libido, depression, sweating and change in breast size. Clinical studies in endometriosis suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established [*see Dosage and Administration (2.3) and Adverse Reactions (6.5) and (6.7)*].
7. The use of GnRH agonists in women may cause a reduction in bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority of patients.
In patients with a history of prior treatment that may have resulted in bone mineral density loss and/or in patients with major risk factors for decreased bone mineral density such as chronic alcohol abuse and/or tobacco abuse, significant family history of osteoporosis, or chronic use of drugs that can reduce bone density such as anticonvulsants or corticosteroids, ZOLADEX therapy may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with ZOLADEX is instituted [*see Adverse Reactions (6.10)*].
8. Currently, there are no clinical data on the effects of retreatment or treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months [*see Dosage and Administration (2.3)*].
9. As with other hormonal interventions that disrupt the pituitary-gonadal axis, some patients may have delayed return to menses. The rare patient, however, may experience persistent amenorrhea [*see Drug Interactions (7.1) and Clinical Studies (14.3) and (14.4)*].

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NDA 020578/S-032

Zoladex (goserelin acetate
implant) 10.8 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOLADEX safely and effectively. See full prescribing information for ZOLADEX.

ZOLADEX® (goserelin acetate implant) 10.8 mg

Initial U.S. Approval: 1996

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions, Hyperglycemia and Diabetes (5.3), 12/2010

Warnings and Precautions, Cardiovascular Diseases (5.4), 12/2010

-----**INDICATIONS AND USAGE**-----

ZOLADEX is a Gonadotropin Releasing Hormone (GnRH) agonist indicated for:

- Use in combination with flutamide for the management of locally confined carcinoma of the prostate (1.1)
- Use as palliative treatment of advanced carcinoma of the prostate (1.2)

-----**DOSAGE AND ADMINISTRATION**-----

ZOLADEX, at a dose of 10.8 mg, should be administered subcutaneously every 12 weeks into the anterior abdominal wall below the navel line (2.1 - 2.5)

-----**DOSAGE FORMS AND STRENGTHS**-----

Implant 10.8 mg (3)

-----**CONTRAINDICATIONS**-----

- Hypersensitivity (4.1)
- Pregnancy (4.2 and 8.1)

-----**WARNINGS AND PRECAUTIONS**-----

- Tumor Flare Phenomenon: Transient worsening of tumor symptoms may occur during the first few weeks of treatment with ZOLADEX, which may include ureteral obstruction and spinal cord compression. Monitor patients at risk for complications of tumor flare. (5.1 and 6.1)
- Hypersensitivity: Systemic hypersensitivity has been reported in patients receiving goserelin implants. (4.1, 5.2 and 6.1)

- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (5.3)
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice. (5.4)

-----**ADVERSE REACTIONS**-----

The most common, clinically significant adverse reactions occurring in >10% of men: hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms. (6)

Tumor flare can occur on the initiation of ZOLADEX therapy. (5.1 and 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.

-----**DRUG INTERACTIONS**-----

- None

-----**USE IN SPECIFIC POPULATIONS**-----

- Nursing mothers: Discontinue drug or nursing taking into account the importance of drug to the mother (8.3)
- No information available for use in Pediatric Patients (8.4)
- Geriatric (8.5)
- Renal and Hepatic Impairment: No dose adjustment is necessary (2.3, 8.6 and 8.7)

-----**SEE 17 FOR PATIENT COUNSELING INFORMATION**-----

Revised 12/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Stage B2-C Prostatic Carcinoma

ZOLADEX is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with ZOLADEX and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy [see *Dosage and Administration (2.1) and Clinical Studies (14.1)*].

1.2 Prostatic Carcinoma

ZOLADEX is indicated in the palliative treatment of advanced carcinoma of the prostate [see *Dosage and Administration (2.2) and Clinical Studies (14.2)*].

In controlled studies of patients with advanced prostatic cancer comparing ZOLADEX 3.6 mg to orchiectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the two treatment arms in a major comparative trial.

In controlled studies of patients with advanced prostatic cancer, ZOLADEX 10.8 mg implant produced pharmacodynamically similar effect in terms of suppression of serum testosterone to that achieved with ZOLADEX 3.6 mg implant. Clinical outcome similar to that produced with the use of the ZOLADEX 3.6 mg implant administered every 28 days is predicted with the ZOLADEX 10.8 mg implant administered every 12 weeks.

The automatic safety feature of the syringe aids in the prevention of needlestick injury.

2 DOSAGE AND ADMINISTRATION

ZOLADEX, at a dose of 10.8 mg, should be administered subcutaneously every 12 weeks into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician [see *Dosage and Administration (2.5)*].

While a delay of a few days is permissible, every effort should be made to adhere to the 12-week schedule.

2.1 Stage B2-C Prostatic Carcinoma

When ZOLADEX is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using one ZOLADEX 3.6 mg depot, followed in 28 days by one ZOLADEX 10.8 mg depot, should be administered.

2.2 Prostatic Carcinoma

For the management of advanced prostate cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

2.3 Renal or Hepatic Impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment.

2.4 Women

ZOLADEX 10.8 mg implant is not indicated in women as the data are insufficient to support reliable suppression of serum estradiol. For female patients requiring treatment with goserelin, refer to prescribing information for ZOLADEX 3.6 mg implant.

2.5 Administration Technique

The proper method of administration of ZOLADEX is described in the instructions that follow.

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.
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 implant is visible.
3. Grasp the blue plastic safety tab and pull away from the syringe, and discard. Remove needle cover. **Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the ZOLADEX implant.**
4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the skin of the patient's anterior abdominal wall below the navel line. With the bevel of the needle facing up, **insert the needle at a 30 to 45 degree angle to the skin** in one continuous deliberate motion until the protective sleeve touches the patient's skin.

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 inject with a new syringe elsewhere.

5. Do not penetrate into muscle or peritoneum.
6. To administer the ZOLADEX implant and to activate the protective sleeve, grasp the barrel at the finger grip and depress the plunger until you cannot depress it any further. If the plunger is not depressed **fully**, the protective sleeve will **NOT** activate. When the protective sleeve 'clicks', the protective sleeve will automatically begin to slide to cover the needle.

NOTE: The needle does not retract.

7. Withdraw the needle and allow protective sleeve 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 ZOLADEX, it may be localized by ultrasound.

3 DOSAGE FORMS AND STRENGTHS

ZOLADEX 10.8 mg implant is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (12.82-14.76 mg/dose) impregnated with goserelin acetate equivalent to 10.8 mg of goserelin in a disposable syringe device fitted with a 14-gauge x 36 +/- 0.5 mm hypodermic siliconized needle with protective needle sleeve [SafeSystem™ Syringe] (NDC 0310-0951-30).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Anaphylactic reactions to ZOLADEX have been reported in the medical literature. ZOLADEX is contraindicated in those patients who have a known hypersensitivity to GnRH, GnRH agonist analogues or any of the components in ZOLADEX.

4.2 Pregnancy

Expected hormonal changes that occur with ZOLADEX treatment increase the risk for pregnancy loss. ZOLADEX may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Flare Phenomenon

Initially, ZOLADEX, like other GnRH agonists, causes transient increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostatic cancer, may occasionally develop during the first few weeks of ZOLADEX treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other GnRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed. If spinal cord compression or renal impairment secondary to ureteral obstruction develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy [*see Adverse Reactions (6.1) and Patient Counseling Information (17.1)*].

5.2 Hypersensitivity

Hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with GnRH agonist analogues [*see Contraindications (4.1) and Adverse Reactions (6.5)*].

Of 115 women worldwide treated with ZOLADEX and tested for development of binding to goserelin following treatment with ZOLADEX, one patient showed low-titer binding to goserelin. On further testing of this patient's plasma obtained following treatment, her goserelin binding component was found not to be precipitated with rabbit antihuman immunoglobulin polyvalent sera. These findings suggest the possibility of antibody formation.

5.3 Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes [*see Adverse Reactions (6.5) and Patient Counseling Information (17.1)*].

5.4 Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice [*see Patient Counseling Information (17.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials

ZOLADEX has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients' withdrawal from ZOLADEX treatment. As seen with other hormonal therapies, the most commonly observed adverse events during ZOLADEX therapy were due to the expected physiological effects from decreased testosterone levels. These included hot flashes, sexual dysfunction and decreased erections.

Tumor Flare Phenomenon: Initially, ZOLADEX, like other GnRH agonists, causes transient increases in serum levels of testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms, usually manifested by an increase in cancer-related pain which was managed symptomatically. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both ZOLADEX and orchiectomy. The relationship of these events to therapy is uncertain [see *Warnings and Precautions (5.1) and Patient Counseling Information (17.1)*].

6.2 Stage B2-C Prostatic Carcinoma

Treatment with ZOLADEX and flutamide did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing ZOLADEX + flutamide + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below:

Table 1 ADVERSE EVENTS DURING ACUTE RADIATION THERAPY (within first 90 days of radiation therapy)

	(n=231)	(n = 235)
	flutamide + ZOLADEX + Radiation	Radiation Only
	% All	% All
Rectum/Large Bowel	80	76
Bladder	58	60
Skin	37	37

Table 2 ADVERSE EVENTS DURING LATE RADIATION PHASE (after 90 days of radiation therapy)

	(n=231)	(n = 235)
	flutamide + ZOLADEX + Radiation	Radiation Only
	% All	% All
Diarrhea	36	40
Cystitis	16	16
Rectal Bleeding	14	20
Proctitis	8	8

	(n=231)	(n = 235)
	flutamide + ZOLADEX + Radiation	Radiation Only
	% All	% All
Hematuria	7	12

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

6.3 Prostatic Carcinoma

Two controlled clinical trials using ZOLADEX 10.8 mg versus ZOLADEX 3.6 mg were conducted. During a comparative phase, patients were randomized to receive either a single 10.8 mg implant or three consecutive 3.6 mg implants every 4 weeks over weeks 0-12. During this phase, the only adverse event reported in greater than 5% of patients was hot flashes, with an incidence of 47% in the ZOLADEX 10.8 mg group and 48% in the ZOLADEX 3.6 mg group.

From weeks 12-48 all patients were treated with a 10.8 mg implant every 12 weeks. During this noncomparative phase, the following adverse events were reported in greater than 5% of patients:

Table 3 Adverse Events were reported in greater than 5% of Patients

Adverse Event	ZOLADEX 10.8 mg (n=157) %
Hot Flashes	64
Pain (general)	14
Gynecomastia	8
Pelvic Pain	6
Bone Pain	6
Asthenia	5

The following adverse events were reported in greater than 1%, but less than 5% of patients treated with ZOLADEX 10.8 mg implant every 12 weeks. Some of these are commonly reported in elderly patients.

WHOLE BODY – Abdominal pain, Back pain, Flu syndrome, Headache, Sepsis, Aggravation reaction

CARDIOVASCULAR – Angina pectoris, Cerebral ischemia, Cerebrovascular accident, Heart failure, Pulmonary embolus, Varicose veins

DIGESTIVE – Diarrhea, Hematemesis

ENDOCRINE – Diabetes mellitus

HEMATOLOGIC – Anemia

METABOLIC –Peripheral edema

NERVOUS SYSTEM – Dizziness, Paresthesia, Urinary retention

RESPIRATORY – Cough increased, Dyspnea, Pneumonia

SKIN – Herpes simplex, Pruritus

UROGENITAL – Bladder neoplasm, Breast pain, Hematuria, Impotence, Urinary frequency, Urinary incontinence, Urinary tract disorder, Urinary tract infection, Urination impaired

The following adverse events not already listed above were reported in patients receiving ZOLADEX 3.6 mg in other clinical trials. Inclusion does not necessarily represent a causal relationship to ZOLADEX 10.8 mg.

WHOLE BODY: Allergic reaction, Chills, Fever, Infection, Injection site reaction, Lethargy, Malaise

CARDIOVASCULAR: Arrhythmia, Chest pain, Hemorrhage, Hypertension, Migraine, Myocardial infarction, Palpitations, Peripheral vascular disorder, Tachycardia

DIGESTIVE: Anorexia, Constipation, Dry mouth, Dyspepsia, Flatulence, Increased appetite, Nausea, Ulcer, Vomiting

HEMATOLOGIC: Ecchymosis

METABOLIC: Edema, Gout, Hyperglycemia, Weight increase

MUSCULOSKELETAL: Arthralgia, Hypertonia, Joint disorder, Leg cramps, Myalgia, Osteoporosis

NERVOUS SYSTEM: Anxiety, Depression, Emotional lability, Headache, Insomnia, Nervousness, Somnolence, Thinking abnormal

RESPIRATORY: Bronchitis, Chronic obstructive pulmonary disease, Epistaxis, Rhinitis, Sinusitis, Upper respiratory infection, Voice alterations

SKIN: Acne, Alopecia, Dry skin, Hair disorders, Rash, Seborrhea, Skin discoloration, Sweating

SPECIAL SENSES: Amblyopia, Dry eyes

UROGENITAL: Breast tenderness, Decreased erections, Renal insufficiency, Sexual dysfunction, Urinary obstruction

6.4 Changes in Laboratory Values During Treatment

Plasma Enzymes: Elevation of liver enzymes (AST, ALT) have been reported in female patients exposed to ZOLADEX 3.6 mg (representing less than 1% of all 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 in females, ZOLADEX 3.6 mg implant therapy resulted in a minor, but statistically significant effect on serum lipids (i.e., increases in LDL cholesterol of 21.3 mg/dL; increases in HDL cholesterol of 2.7 mg/dL; and triglycerides increased by 8.0 mg/dL).

6.5 Post-Marketing

Hypersensitivity: Rarely, hypersensitivity reactions (including urticaria and anaphylaxis) have been reported in patients receiving ZOLADEX [see *Contraindications (4.1) and Warnings and Precautions (5.2)*].

Hypercalcemia: As with other endocrine therapies, hypercalcemia (increased calcium) has rarely been reported in cancer patients with bone metastases following initiation of treatment with ZOLADEX or other GnRH agonists.

Bone Mineral Density: There have been post-marketing reports of osteoporosis, decreased bone mineral density and bony fracture in men treated with ZOLADEX for prostate cancer [see *Patient Counseling Information (17.1)*].

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

Pituitary Apoplexy and Tumors: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed. Most of the pituitary apoplexy cases occurred within 2 weeks of the first dose, and some occurred within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required. Very rare cases of pituitary tumors have been reported.

Glucose Tolerance: Reduction in glucose tolerance, manifesting as diabetes or loss of glycemic control in those with pre-existing diabetes, has been reported during treatment with GnRH agonists, including ZOLADEX [see *Warnings and Precautions (5.3) and Patient Counseling Information (17.1)*].

Other Adverse Reactions: Psychotic disorders have also been reported.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed.

No drug interaction studies with other drugs have been conducted with ZOLADEX. No confirmed interactions have been reported between ZOLADEX and other drugs.

7.1 Drug/Laboratory Test Interactions

Administration of ZOLADEX in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment may show results which are misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies, ZOLADEX may cause fetal harm when administered to a pregnant woman. Expected hormone changes that occur with ZOLADEX treatment increase the risk for pregnancy loss. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Contraindications (4.2)*].

ZOLADEX crosses the placenta in rats and rabbits following subcutaneous administration. Administration of goserelin to pregnant rats and rabbits during organogenesis resulted in increased preimplantation loss and increased resorptions. When pregnant rats received goserelin throughout gestation and lactation, there was a dose-related increase in umbilical hernia in offspring. In additional reproduction studies in rats, goserelin decreased fetus and pup survival. Human dose/exposure multiples could not be calculated from available animal data.

Actual animal doses: rat (≥ 2 mcg/kg/day for pregnancy loss; ≥ 10 mcg/kg/day for umbilical hernia in offspring); rabbits (> 20 mcg/kg/day).

8.3 Nursing Mothers

It is not known if goserelin is excreted in human milk. Goserelin is excreted in the milk of lactating rats. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZOLADEX, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There is no need for any dosage adjustment when administering ZOLADEX 10.8 mg to geriatric patients.

8.6 Renal Insufficiency

In clinical trials with the solution formulation of goserelin, subjects with impaired renal function (creatinine clearance < 20 mL/min) had a serum elimination half-life of 12.1 hours compared to 4.2 hours for subjects with normal renal function (creatinine clearance > 70 mL/min). However, there was no evidence for any accumulation of goserelin on multiple dosing of the ZOLADEX 10.8 mg depot to subjects with impaired renal function. There was no evidence for any increase in incidence of adverse events in renally impaired patients administered the 10.8 mg depot. These data indicate that there is no need for any dosage adjustment when administering ZOLADEX 10.8 mg to subjects with impaired renal function.

8.7 Hepatic Insufficiency

The total body clearances and serum elimination half-lives were similar between normal subjects and patients with moderate hepatic impairment (alanine transaminase < 3xULN and aspartate aminotransferase < 3xULN) when treated with a 250 mcg subcutaneous formulation of goserelin. This pharmacokinetic study indicates that no dose adjustment is needed in patients with moderately impaired liver function. There is no pharmacokinetic data with goserelin in patients with severe hepatic insufficiency.

8.8 Body Weight

A decline of approximately 1 to 2.5% in the AUC after administration of a 10.8 mg depot was observed with a kilogram increase in body weight. In obese patients who have not responded clinically, testosterone levels should be monitored closely.

10 OVERDOSAGE

The pharmacologic properties of ZOLADEX and its mode of administration make accidental or intentional overdosage unlikely. There is no experience of overdosage from clinical trials. Animal studies indicate that no increased pharmacologic effect occurred at higher doses or more frequent administration. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs did not produce any nonendocrine related sequelae; this dose is up to 250 times the estimated human daily dose based on the body surface area. If overdosage occurs, it should be managed symptomatically.

11 DESCRIPTION

ZOLADEX® (goserelin acetate implant) is a GnRH agonist. Goserelin acetate is chemically described as an acetate salt of [D-Ser(Bu^t)₆,Azgly¹⁰]. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro-Azgly-NH₂ acetate [C₅₉H₈₄N₁₈O₁₄ ·(C₂H₄O₂)_x where x = 1 to 2.4].

Goserelin acetate is an off-white powder with a molecular weight of 1269 Daltons (free base). It is freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform and ether.

ZOLADEX 10.8 mg implant is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 10.8 mg of goserelin. ZOLADEX is designed for subcutaneous implantation with continuous release over a 12-week period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82-14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white to cream colored 1.5 mm diameter cylinder, preloaded in a special single-use syringe with a 14-gauge x 36 +/- 0.5 mm siliconized needle with protective needle sleeve (SafeSystem™ Syringe) in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.

Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

ZOLADEX is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin designed for administration every 28 days.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZOLADEX is a synthetic decapeptide analogue of GnRH. ZOLADEX acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation.

In animal and *in vitro* studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor.

12.2 Pharmacodynamics

Following initial administration, ZOLADEX causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of ZOLADEX leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 21 days after initiation of therapy. This leads to accessory sex organ regression.

In clinical trials using ZOLADEX 3.6 mg with follow-up of more than 2 years, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of ZOLADEX have been determined in healthy male volunteers and patients. In healthy males, radiolabeled goserelin was administered as a single 250 mcg (aqueous solution) dose by the subcutaneous route. The absorption of radiolabeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing.

The overall pharmacokinetic profile of goserelin following administration of a ZOLADEX 10.8 mg depot to patients with prostate cancer was determined. The initial release of goserelin from the depot was relatively rapid resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin from the depot produced reasonably stable systemic exposure. Mean (Standard Deviation) pharmacokinetic data are presented in Table 4. There is no clinically significant accumulation of goserelin following administration of four depots administered at 12-week intervals.

Table 4 - Goserelin pharmacokinetic parameters for the 10.8 mg depot

Parameter	N	Mean	(SD)
Systemic clearance (mL/min)	41	121	(42.4)
Cmax (ng/mL)	41	8.85	(2.83)
Tmax (h)	41	1.80	(0.34)
Cmin (ng/mL)	44	0.37	(0.21)

SD = standard deviation

Serum goserelin concentrations in prostate cancer patients administered three 3.6 mg depots followed by one 10.8 mg depot are displayed in Figure 1. The profiles for both formulations are primarily dependent upon the rate of drug release from the depots. For the 3.6 mg depot, mean concentrations gradually rise to reach a peak of about 3 ng/mL at around 15 days after administration and then decline to approximately 0.5 ng/mL by the end of the treatment period. For the 10.8 mg depot, mean concentrations increase to reach a peak of about 8 ng/mL within the first 24 hours and then decline rapidly up to Day 4. Thereafter, mean concentrations remain relatively stable in the range of about 0.3 to 1 ng/mL up to the end of the treatment period.

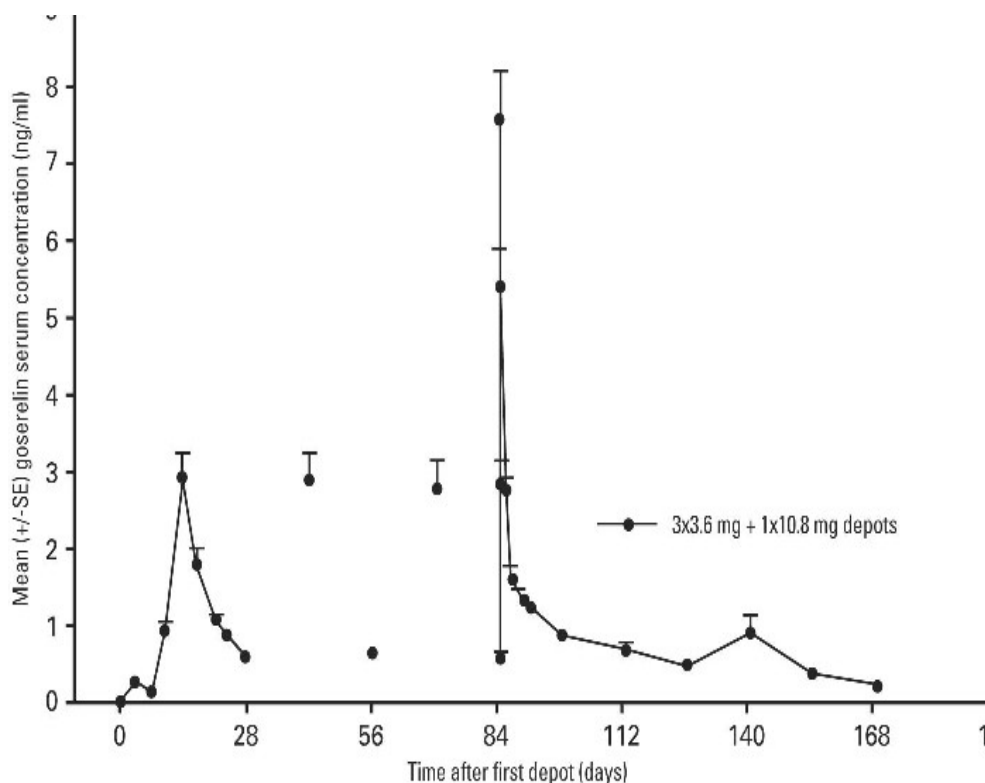


Figure 1: Goserelin serum concentrations during dosing three ZOLADEX 3.6 mg depots (0, 28, 56 days) then one ZOLADEX 10.8 mg depot (84 days) to prostate cancer patients.

Administration of four ZOLADEX 10.8 mg depots to patients with prostate cancer resulted in testosterone levels that were suppressed to and maintained within the range normally observed in surgically castrated men (0 - 1.73 nmol/L or 0-50 ng/dL), over the dosing interval in approximately 91% (145/160) of patients studied. In 6 of 15 patients that escaped from castrate range, serum testosterone levels were maintained below 2.0 nmol/L (58 ng/dL) and in only one of the 15 patients did the depot completely fail to maintain serum testosterone levels to within the castrate range over a 336-day period (4 depot injections). In the 8 additional patients, a transient escape was followed 14 days later by a level within the castrate range.

Distribution

The apparent volume of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin was 44.1 ± 13.6 liters for healthy males. The plasma protein binding of goserelin was found to be 27%.

Metabolism

Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component present in urine of one healthy male volunteer was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion

Clearance of goserelin following subcutaneous administration of a radiolabeled solution of goserelin was very rapid and occurred via a combination of hepatic and urinary excretion. More than 90% of a subcutaneous radiolabeled solution formulation dose of goserelin was excreted in urine. Approximately 20% of the dose recovered in urine was accounted for by unchanged goserelin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Subcutaneous implantation of goserelin in male and female rats once every 4 weeks for 1 year and recovery for 23 weeks at doses of about 80 and 150 mcg/kg (males) and 50 and 100 mcg/kg (females) daily resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following subcutaneous implant of goserelin in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females. The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of goserelin every 3 weeks for 2 years delivered to mice at doses of up to 2400 mcg/kg/day resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur. Human dose/exposure multiples could not be calculated from available animal data.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 mcg/kg/day, a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 mcg/kg/day, suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the testes, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs were reversible in male and female dogs administered 107-214 mcg/kg/day goserelin when drug treatment was stopped after continuous administration for 1 year. Human dose/exposure multiples could not be calculated from available animal data.

14 CLINICAL STUDIES

14.1 Stage B2-C Prostatic Carcinoma

The effects of hormonal treatment combined with radiation were studied in 466 patients (231 ZOLADEX + flutamide + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of ZOLADEX (3.6 mg depot) and flutamide capsules (250 mg t.i.d.) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years, $P < 0.001$). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, $P = 0.058$). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, $P < 0.001$). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, $P < 0.001$).

14.2 Prostatic Carcinoma

In two controlled clinical trials, 160 patients with advanced prostate cancer were randomized to receive either one 3.6 mg ZOLADEX implant every four weeks or a single 10.8 mg ZOLADEX implant every 12 weeks. Mean serum testosterone suppression was similar between the two arms. PSA falls at three months were 94% in patients who received the 10.8 mg implant and 92.5% in patients that received three 3.6 mg implants.

Periodic monitoring of serum testosterone levels should be considered if the anticipated clinical or biochemical response to treatment has not been achieved. A clinical outcome similar to that produced with the use of the 3.6 mg implant administered every 28 days is predicted with ZOLADEX 10.8 mg implant administered every 12 weeks (84 days). Total testosterone was measured by the DPC Coat-A-Count radioimmunoassay method which, as defined by the manufacturers, is highly specific and accurate. Acceptable variability of approximately 20% at low testosterone levels has been demonstrated in the clinical studies performed with the ZOLADEX 10.8 mg depot.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOLADEX 10.8 mg implant is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (12.82-14.76 mg/dose) impregnated with goserelin acetate equivalent to 10.8 mg of goserelin in a disposable syringe device fitted with a 14-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective sleeve (SafeSystem™ Syringe) (NDC 0310-0951-30). The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C [77°F]).

17 PATIENT COUNSELING INFORMATION

17.1 Males

The use of ZOLADEX in patients at particular risk of developing ureteral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. Patients with ureteral obstruction or spinal cord compression should have appropriate treatment prior to initiation of ZOLADEX therapy [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

The use of GnRH agonists may cause a reduction in bone mineral density. In men, data suggest the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss [*see Adverse Reactions (6.5)*].

Patients should be informed that diabetes, or loss of glycemic control in patients with pre-existing diabetes, has been reported during treatment with GnRH agonists, including ZOLADEX. Therefore, consideration should be given to monitoring blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving ZOLADEX [*see Warnings and Precautions (5.3) and Adverse Reactions (6.5)*].

A small increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice [*see Warnings and Precautions (5.4)*].

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