ZOLADEX® (goserelin acetate implant) 10.8 mg

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Stage B2-C Prostatic Carcinoma
1.2 Prostate Carcinoma

2 DOSAGE AND ADMINISTRATION
2.1 Stage B2-C Prostatic Carcinoma
2.2 Prostatic Carcinoma
2.3 Renal or Hepatic Impairment
2.4 Women
2.5 Administration Technique

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
4.1 Hypersensitivity
4.2 Pregnancy

5 WARNINGS AND PRECAUTIONS
5.1 Tumor Flare Phenomenon
5.2 Women
5.3 Hyperglycemia and Diabetes

6 ADVERSE REACTIONS
6.1 Clinical Trials
6.2 Stage B2-C Prostatic Carcinoma
6.3 Prostatic Carcinoma
6.4 Changes in Laboratory Values During Treatment
6.5 Postmarketing Experience

7 DRUG INTERACTIONS
7.1 Drug/Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Nursing Mothers
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Renal Insufficiency

9 NURSING MOTHERS

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Stage B2-C Prostatic Carcinoma
14.2 Prostatic Carcinoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
17.1 Males

* Sections or subsections omitted from the full prescribing information are not listed.
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.
2. Prepare an area of the anterior abdominal wall below the navel line with an alcoholic swab.
   NOTE: Caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferolateral epigastric artery and its branches.
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 makes contact with 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. Monitor patients for signs or symptoms of abdominal hemorrhage. Use extra care when administering ZOLADEX to patients with a low BMI and/or to patients receiving full dose anticoagulation [see Warnings and Precautions (5.6)].
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-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 70720-951-30).

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 agonists or any of the components in ZOLADEX [see Warnings and Precautions (5.2)].

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 apprised 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)].

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 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 Effect on QT/QTc Interval
Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

5.6 Injection Site Injury
Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with ZOLADEX. Extra care should be taken when administering ZOLADEX to patients with a low BMI and/or to patients receiving full anticoagulation [see Dosage and Administration (2.5) and 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 orchietomy. 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 therapy 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)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>(n=231) flutamide + ZOLADEX + Radiation</th>
<th>(n=235) Radiation Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Cystitis</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Rectal Bleeding</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>Proctitis</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7%</td>
<td>12%</td>
</tr>
</tbody>
</table>

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 comparability 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 3% of patients:

Table 3: ADVERSE EVENTS WERE REPORTED IN GREATER THAN 5% OF PATIENTS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ZOLADEX 10.8 mg (n=137) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flashes</td>
<td>64%</td>
</tr>
<tr>
<td>Pain (general)</td>
<td>14%</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>8%</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>6%</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>6%</td>
</tr>
<tr>
<td>Asthma</td>
<td>5%</td>
</tr>
</tbody>
</table>
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.

8.3 Nursing Mothers

It is not known if goserelin is excreted in human milk. Goserelin is excreted in the milk of lactating animals. Because of many similarities between human and animal 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 patients with severe hepatic insufficiency.

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 < 5xULN) 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.

10.12 OVERDOSAGE

The pharmacologic properties of ZOLADEX and its mode of administration make accidental or intentional overdose unlikely. There is no experience of overdose 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 in dogs and rats 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)²-Pro-NH₂]-leucine (Bu-Leu-Pro-NH₂) acetate (C₁₇H₃₇NO₃·(CH₃CO₂H), 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 white, sterile to white cream colored 1.5 mm diameter cylinder, preload in a special single-use syringe with a 14-gauge × 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 for design administration every 28 days.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZOLADEX is a synthetic decapetide 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 Dunn 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, radioabeled goserelin was administered as a single 250 mcg (aqueous solution) dose by the subcutaneous route. The absorption of radioabeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing.

Drug interaction studies of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunn R3327 prostate tumor.
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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mean</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic clearance (mL/min)</td>
<td>41</td>
<td>121</td>
<td>(42.4)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>41</td>
<td>8.85</td>
<td>(2.83)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>41</td>
<td>1.80</td>
<td>(0.34)</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>44</td>
<td>0.37</td>
<td>(0.21)</td>
</tr>
</tbody>
</table>

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.

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 that were 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 pathway of goserelin. The major metabolite of goserelin is the C-18 fragment. The hydrolysis 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 toxicity 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 TOXICITY

#### 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 implantation 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.