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1.2 Prostatic Carcinoma
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17.1 Males

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Stage B2-C Prostatic Carcinoma
ZOLADEX® (goserelin acetate implant) 10.8 mg 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 for use in combination with flutamide for the management of locally confined carcinoma of the prostate (1.1).

2 DOSAGE AND ADMINISTRATION

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.

3 DOSAGE FORMS AND STRENGTHS

Implant 10.8 (3)

4 CONTRAINDICATIONS

4.1 Hypersensitivity
4.2 Pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Flare Phenomenon

5.2 Hypersensitivity: Systemic hypersensitivity has been reported in patients receiving goserelin implants (4.1, 5.2)

5.3 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)

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

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2.2 Prostatic Carcinoma

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

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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.

3 DOSAGE FORMS AND STRENGTHS

Implant 10.8 (3)

4 CONTRAINDICATIONS

4.1 Hypersensitivity
4.2 Pregnancy

5 WARNINGS AND PRECAUTIONS

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 (5.1, 6.1)

5.2 Hypersensitivity: Systemic hypersensitivity has been reported in patients receiving goserelin implants (4.1, 5.2)

5.3 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)

6 ADVERSE REACTIONS

6.1 Clinical Trials

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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.

2. Prepare an area of the anterior abdominal wall below the navel line with an alcohol swab.

NOTE: Caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying intraepigastric artery and its branches.

3. 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.

4. 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.

5. 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. 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 anticogulation (see Warnings and Precautions (5.6)).

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 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 agonist analogues 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 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)).

5.2 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)).

5.3 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 dose anticogulation (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 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 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>Rectal/Large Bowel</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Bladder</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Skin</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 2 ADVERSE EVENTS DURING LATE RADIATION PHASE (after 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 (4%), diarrhea (4%), 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 comparator 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 10.8mg (n=157)</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>Asthenia</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.


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


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 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZOLADEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypercalcemia: In patients with bone metastases. Bone Mineral Density: Osteoporosis, decreased bone mineral density and bone fracture in men [see Patient Counseling Information (17.1)]. Changes in Blood Pressure: Hypotension and hypertension have been reported. These changes are usually transient, resolving either during continued therapy or after cessation of therapy. Pituitary Apoplexy and Tumors: Pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) and pituitary adenoma have been diagnosed. Most of the pituitary apoplexy cases occurred during 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. Pituitary tumors have been reported. Acne: Usually within one month of starting treatment.

Other Adverse Reactions: Psychotic disorders, convulsions and mood swings.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed. No drug interaction studies with other drugs have been conducted with ZOLADEX. It is not known if ZOLADEX is involved in the metabolism of other drugs by cytochrome P450 enzymes.

ZOLADEX is also supplied as a sterile, biodegradable product containing goserelin acetate 10.8 mg and a D,L-lactic and glycolic acids copolymer. The copolymer is completely biodegraded in the body to carbon dioxide and water. The polymer has been shown to be biocompatible in in vivo animal studies.

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 is embryo/fetal toxic. There is no evidence of a causal relation between ZOLADEX and human pregnancy loss or congenital anomalies. Goserelin acetate changes 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 addition, 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 <3×ULN and aspartate aminotransferase <3×ULN) when treated with a 250 mcg subcutaneous formulation of goserelin acetate. 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 noncortinone 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
H)
-Tyr(Tos)-Ala-Pro-Thr-Glu-His-Trp-Ser(Tyr)-D-Ser(Bu
)-Leu-Pro-Arg-Pro-Acyl NH acetate (C
5
H
10
N
2
O
5
), 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 (goserelin acetate implant) is a GnRH agonist. Goserelin acetate is chemically described as an acetate salt of [D-Ser(Bu
H)
-Tyr(Tos)-Ala-Pro-Thr-Glu-His-Trp-Ser(Tyr)-D-Ser(Bu
)-Leu-Pro-Arg-Pro-Acyl NH acetate (C
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ZOLADEX 10.8 mg implant is 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 decapetide analogue of GnRH. ZOLADEX acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. In animals and in vivo studies, administration of goserelin resulted in the regression or inhibition of growth of the hormone sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunn's R3327 prostate tumor.

12.2 Pharmacodynamics

Following initial administration, ZOLADEX causes a consistent increase in serum lutinizing 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.
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 (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic clearance (mL/min)</td>
<td>41</td>
<td>121 (42.4)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>41</td>
<td>8.85 (2.83)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>41</td>
<td>1.80 (0.34)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>44</td>
<td>0.37 (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 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.

**Figure 1:** Goserelin serum concentrations during dosing three ZOLADEX 3.6 mg depots (0, 28, 56 days) then one 10.8 mg depot (92 days) followed by one 10.8 mg depot (168 days) in prostate cancer patients.

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 component present in urine of one healthy male volunteer was 27% of the administered dose. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. The metabolism of goserelin was very rapid and occurred via a combination of hepatic and urinary excretion. More than 90% of an oral dose of goserelin was recovered in urine within 72 hours. The major metabolites were 5-10 fragment. The metabolism of goserelin was found to be 27%.

### Excretion

Clearance of goserelin following subcutaneous administration of a radioabeled solution of goserelin was very rapid and occurred via a combination of hepatic and urinary excretion. More than 90% of a subcutaneous radioabeled 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.