HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELIGARD® safely and effectively. See full prescribing information for ELIGARD®.

ELIGARD® (leuprolide acetate for injectable suspension)
Initial U.S. Approval: 2002

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

Dosage and Administration (2)	10/2014
Warnings and Precautions (5.5)	10/2014

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

ELIGARD® is a gonadatropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer (1)

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

- 7.5 mg subcutaneously every month (2)
- 22.5 mg subcutaneously every 3 months (2)
- 30 mg subcutaneously every 4 months (2)
- 45 mg subcutaneously every 6 months (2)

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

- Injectable suspension: 7.5 mg (3)
- Injectable suspension: 22.5 mg (3)
- Injectable suspension: 30 mg (3)
- Injectable suspension: 45 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD® (4.1)
- Pregnancy (4.2)

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

- Tumor Flare; Transient increase in serum levels of testosterone during treatment may result in worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, bladder outlet obstruction, ureteral obstruction, or spinal cord compression. Monitor patients at risk closely and manage as appropriate (5.1, 5.2)
- 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 men. Monitor for cardiovascular disease and manage according to current clinical practice (5.4)
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits. (5.5)

----------ADVERSE REACTIONS----------

- Most common adverse reactions in clinical studies (incidence ≥5%): Malaise, fatigue, hot flashes/sweats, and testicular atrophy. (6.1)
- As with other GnRH agonist, other adverse reactions, including decreased bone density and rare cases of pituitary apoplexy have been reported (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact TOLMAR Pharmaceuticals, Inc. at 1-888-354-4273 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Pregnancy: ELIGARD® should not be used in pregnancy (8.1)
- Safety and effectiveness in pediatric patients have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Mixing Procedure
2.2 Administration Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Hypersensitivity
4.2 Pregnancy
5 WARNINGS AND PRECAUTIONS
5.1 Tumor Flare
5.2 Laboratory Tests
5.3 Hyperglycemia and Diabetes
5.4 Cardiovascular Diseases
5.5 Effect on QT/QTc Interval
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Post-marketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
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
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

ELIGARD® is indicated for the palliative treatment of advanced prostate cancer.

2. DOSAGE AND ADMINISTRATION

As with other similar agents, the use of gloves is recommended during mixing and administration.[1]

ELIGARD® is administered **subcutaneously** and provides continuous release of leuprolide acetate over a one-, three-, four-, or six-month treatment period (Table 1). The injection delivers the dose of leuprolide acetate incorporated in a polymer formulation.

Table 1. ELIGARD® Recommended Dosing

Dosage	7.5 mg	22.5 mg	30 mg	45 mg
Recommended dose	1 injection every month	1 injection every 3 months	1 injection every 4 months	1 injection every 6 months

As with other drugs administered by subcutaneous injection, the injection site should vary periodically. The specific injection location chosen should be an area with sufficient soft or loose subcutaneous tissue. In clinical trials, the injection was administered in the upper- or mid-abdominal area. Avoid areas with brawny or fibrous subcutaneous tissue or locations that could be rubbed or compressed (i.e., with a belt or clothing waistband).

2.1 Mixing Procedure

IMPORTANT: Allow the product to reach room temperature before mixing. Once mixed, the product must be administered within 30 minutes or it should be discarded.

Follow the detailed instructions below to ensure proper preparation of ELIGARD® prior to administration:

ELIGARD® is packaged in two thermoformed trays. Each carton contains:

- One sterile syringe (Syringe A) pre-filled with the ATRIGEL® Delivery System
- One sterile syringe (Syringe B) pre-filled with leuprolide acetate powder
- One long white plunger rod for use with Syringe B
- One sterile needle or One sterile safety needle
- Desiccant pack(s)

1. On a clean field, open all of the packages and remove the contents. Discard the desiccant pack(s).

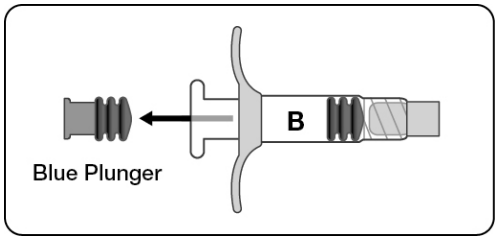


Figure 1

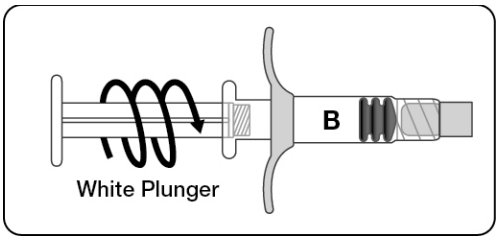


Figure 2

2. **Pull out the short blue plunger rod with attached grey stopper from Syringe B and discard (Figure 1).** Twist the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B (Figure 2).

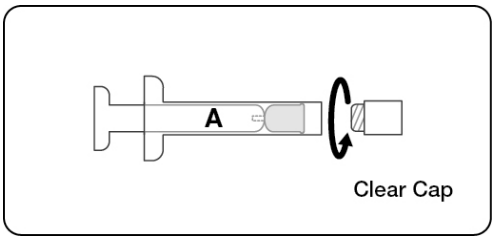


Figure 3

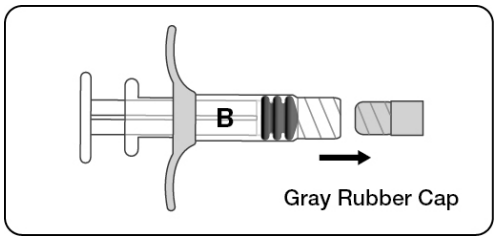


Figure 4

3. Unscrew and discard the clear cap from Syringe A (Figure 3). **Remove and discard the gray rubber cap from Syringe B (Figure 4)**.

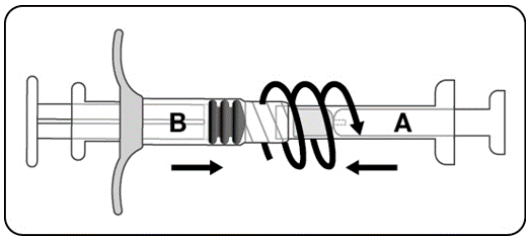


Figure 5

4. Join the two syringes together by pushing and twisting until secure (Figure 5).

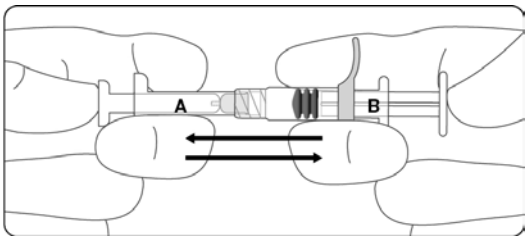


Figure 6

5. Inject the liquid contents of Syringe A into Syringe B that contains the leuprolide acetate powder. Thoroughly mix the product for approximately 45 seconds by pushing the contents back and forth between both syringes to obtain a uniform suspension (Figure 6). When thoroughly mixed, the suspension will appear light tan to tan (ELIGARD® 7.5 mg) or colorless to pale yellow (ELIGARD® 22.5 mg, 30 mg and 45 mg). **Please Note: Product must be mixed as described; shaking will NOT provide adequate mixing of the product.**

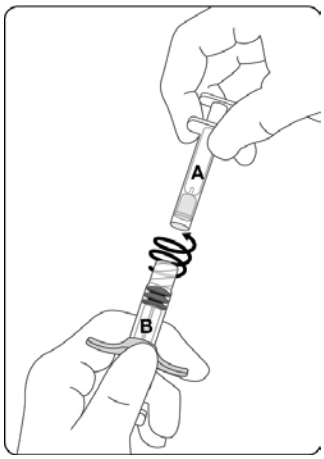


Figure 7

6. After mixing, hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (short, wide syringe) by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger. Unscrew Syringe A to decouple the syringes while continuing to push down on the Syringe A plunger (Figure 7). **Note: Small air bubbles will remain in the formulation – this is acceptable.**

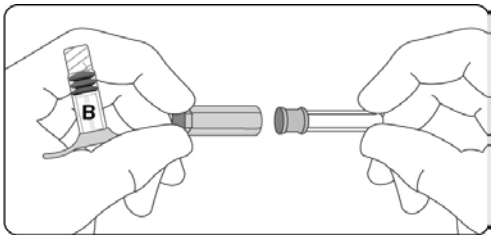


Figure 8

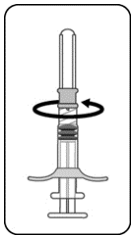


Figure 9

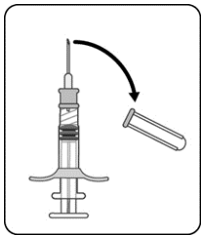


Figure 10

*[Applies to ELIGARD® single use kit of a two syringe-mixing system with **sterile needle**]*

7. Hold Syringe B vertically. Remove and discard the cap on the bottom of the sterile needle cartridge by twisting it (Figure 8). Attach the needle cartridge to the end of

Syringe B (Figure 9) by pushing in and turning the needle until it is firmly seated. Do not overtwist the needle onto the syringe because the thread may become stripped. Pull off the clear needle cartridge cover prior to administration (Figure 10).

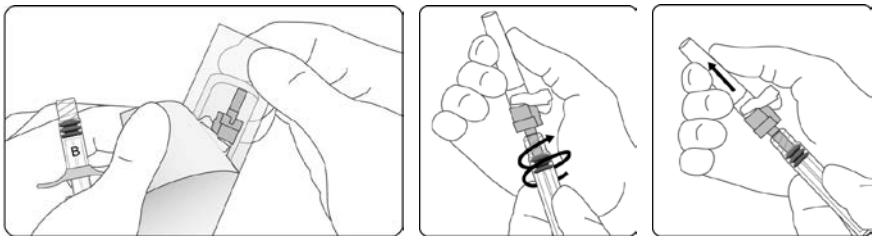


Figure 11 **Figure 12** **Figure 13**

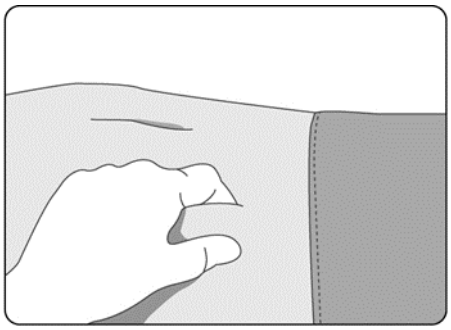
[Applies to ELIGARD® single use kit of a two syringe-mixing system with ***sterile safety needle****]*

8. Hold Syringe B vertically. Open the sterile safety needle package by peeling back the paper tab and remove the safety needle (Figure 11). Secure the needle to the end of Syringe B by holding the protective needle sheath and twisting the syringe clockwise to fully seat the needle (Figure 12). Do not overtwist the needle onto the syringe because the thread may become stripped. Remove the protective needle sheath prior to administration (Figure 13).

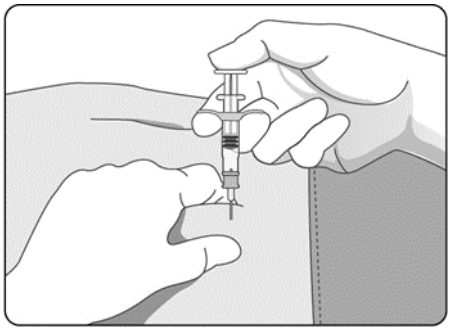
2.2 Administration Procedure

IMPORTANT: Allow the product to reach room temperature before mixing. Once mixed, the product must be administered within 30 minutes or it should be discarded.

1. Choose an injection site on the abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Since you can vary the injection site for **subcutaneous** injections, choose an area that hasn't recently been used.
2. Cleanse the injection-site area with an alcohol swab.



3. Using the thumb and forefinger of your non-dominant hand, grab and bunch the area of skin around the injection site.



4. Using your dominant hand, insert the needle quickly at a 90° angle to the skin surface. The depth of penetration will depend on the amount and fullness of the subcutaneous tissue and the length of the needle. After the needle is inserted, release the skin with your nondominant hand.
5. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.
6. Withdraw the needle quickly at the same 90° angle used for insertion.

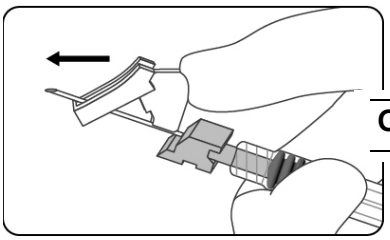


Figure 14

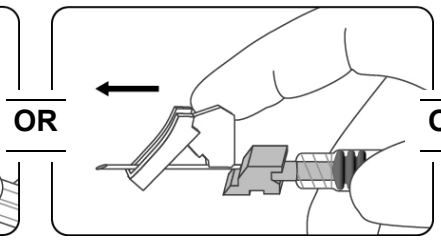


Figure 15

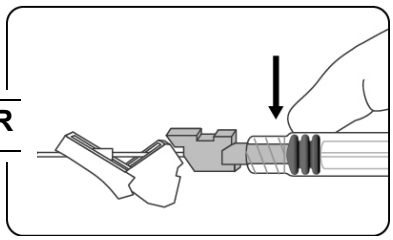


Figure 16

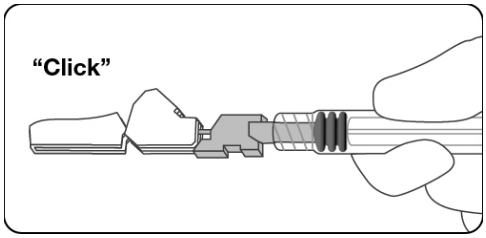


Figure 17

[Step 7 only applies to ELIGARD® single use kit of a two syringe-mixing system with ***sterile safety needle****]*

7. Immediately following the withdrawal of the needle, activate the safety shield on the needle by using a thumb (Figure 14) or finger (Figure 15) or a flat surface (Figure 16) to push the safety shield forward until it completely covers the needle tip and locks into place. An audible and tactile "click" verifies a locked position for the safety shield (Figure 17).
8. Discard all components safely in an appropriate biohazard container.

3. DOSAGE FORMS AND STRENGTHS

ELIGARD® is an injectable suspension of leuprolide acetate available in a single use kit. The kit consists of a two-syringe mixing system, a sterile needle or a sterile safety needle (Table 2), a silica gel desiccant pouch to control moisture uptake, and a package insert for constitution and administration procedures. Each syringe is individually packaged. One contains the ATRIGEL® Delivery System and the other contains leuprolide acetate powder. When constituted, ELIGARD® is administered as a single dose.

Table 2. ELIGARD® Needle specifications

ELIGARD® formulation	Sterile needle		Sterile safety needle	
	Gauge	Length	Gauge	Length
7.5 mg	20-gauge	1/2-inch	20-gauge	5/8-inch
22.5 mg	20-gauge	1/2-inch	20-gauge	5/8-inch
30 mg	20-gauge	5/8-inch	20-gauge	5/8-inch
45 mg	18-gauge	5/8-inch	18-gauge	5/8-inch

4. CONTRAINDICATIONS

4.1 Hypersensitivity

ELIGARD® is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD®. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.

4.2. Pregnancy

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

5. WARNINGS AND PRECAUTIONS

5.1 Tumor Flare

ELIGARD® 7.5 mg 22.5 mg 30 mg, like other GnRH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. ELIGARD® 45 mg causes a transient increase in serum concentrations of testosterone during the first two weeks of treatment. Patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, or bladder outlet obstruction.

Cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been observed in the palliative treatment of advanced prostate cancer using GnRH agonists.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy. If spinal cord compression or ureteral obstruction develops, standard treatment of these complications should be instituted.

5.2 Laboratory Tests

Response to ELIGARD® should be monitored by periodic measurement of serum concentrations of testosterone and prostate specific antigen.

In the majority of patients, testosterone levels increased above Baseline during the first week, declining thereafter to Baseline levels or below by the end of the second or third week. Castrate levels were generally reached within two to four weeks.

Castrate testosterone levels were maintained for the duration of the treatment with ELIGARD® 7.5 mg. No increases to above the castrate level occurred in any of the patients.

Castrate levels were generally maintained for the duration of treatment with ELIGARD® 22.5 mg.

Once castrate levels were achieved with ELIGARD® 30 mg, most (86/89) patients remained suppressed throughout the study.

Once castrate levels were achieved with ELIGARD® 45 mg, only one patient (< 1%) experienced a breakthrough, with testosterone levels > 50 ng/dL.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Drug/Laboratory Test Interactions: Therapy with leuprolide acetate results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide therapy may be affected.

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.

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.

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.

6. ADVERSE REACTIONS

6.1 Clinical trial experience

The safety of all ELIGARD® formulations was evaluated in clinical trials involving patients with advanced prostate cancer. In addition, the safety of ELIGARD® 7.5 mg was evaluated in 8 surgically castrated males (Table 4). ELIGARD®, like other GnRH analogs, caused a transient increase in serum testosterone concentrations during the first one to two weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as

weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms *[see WARNINGS AND PRECAUTIONS (5.2)]*.

During the clinical trials, injection sites were closely monitored. Refer to Table 3 for a summary of reported injection site events.

Table 3. Reported Injection Site Adverse Events

ELIGARD®	**7.5 mg**	**22.5 mg**	**30 mg**	**45 mg**
Study number	AGL9904	AGL9909	AGL0001	AGL0205
Number of patients	120	117	90	111
Treatment	1 injection every month up to 6 months	1 injection every 3 months up to 6 months	1 injection every 4 months up to 8 months	1 injection every 6 months up to 12 months
Number of injections	716	230	175	217
Transient burning/stinging	248 (34.6%) injections;84% reported as mild	50 (21.7%) injections; 86% reported as mild	35 (20%) injections; 100% reported as mild	35 (16%) injections; 91.4% reported as mild[3]
Pain (generally brief and mild)	4.3% of injections (18.3% of patients)	3.5% of injections (6.0% of patients)	2.3% of injections[2] (3.3% of patients)	4.6% of injections[4]
Erythema (generally brief and mild)	2.6% of injections (12.5% of patients)	0.9% of injections[1] (1.7% of patients)	1.1% of injections (2.2% of patients)	
Bruising (mild)	2.5% of injections (11.7% of patients)	1.7% of injections (3.4% of patients)		2.3% of injections[5]
Pruritus	1.4% of injections (9.2% of patients)	0.4% of injections (0.9% of patients)		
Induration	0.4% of injections (2.5% of patients)			
Ulceration	0.1% of injections (> 0.8% of patients)			

1. Erythema was reported following 2 injections of ELIGARD® 22.5 mg. One report characterized the erythema as mild and it resolved within 7 days. The other report characterized the erythema as moderate and it resolved within 15 days. Neither patient experienced erythema at multiple injections.
2. A single event reported as moderate pain resolved within two minutes and all 3 mild pain events resolved within several days following injection of ELIGARD® 30 mg.
3. Following injection of ELIGARD® 30 mg, three of the 35 burning/stinging events were reported as moderate.
4. Transient pain was reported as mild in intensity in nine of ten (90%) events and moderate in intensity in one of ten (10%) events following injection of ELIGARD® 45 mg.
5. Mild bruising was reported following 5 (2.3%) study injections and moderate bruising was reported following 2 (<1%) study injections of ELIGARD® 45 mg.

These localized adverse events were non-recurrent over time. No patient discontinued therapy due to an injection site adverse event.

The following possibly or probably related systemic adverse events occurred during clinical trials with ELIGARD®, and were reported in > 2% of patients (Table 4). Often, causality is

difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

Table 4. Summary of Possible or Probably Related Systemic Adverse Events Reported by > 2% of Patients treated with ELIGARD®

ELIGARD®		**7.5 mg**	**7.5 mg**	**22.5 mg**	**30 mg**	**45 mg**
Study number		AGL9904	AGL9802	AGL9909	AGL0001	AGL0205
Number of patients		120	8	117	90	111
Treatment		1 injection every month up to 6 months	1 injection (surgically castrated patients)	1 injection every 3 months up to 6 months	1 injection every 4 months up to 8 months	1 injection every 6 months up to 12 months
Body system	**Adverse event**	**Number (percent)**				
Body as a whole	Malaise and fatigue	21 (17.5 %)		7 (6.0%)	12 (13.3%)	13 (11.7%)
	Weakness					4 (3.6%)
Nervous system	Dizziness	4 (3.3%)			4 (4.4%)	
Vascular	Hot flashes/sweats	68 (56.7%)*	2 (25.0%)*	66 (56.4%)*	66 (73.3%)*	64 (57.7%)*
Renal/urinary	Urinary frequency			3 (2.6%)	2 (2.2%)	
	Nocturia				2 (2.2%)	
Gastrointestinal	Nausea			4 (3.4%)	2 (2.2%)	
	Gastroenteritis/colitis	3 (2.5%)				
Skin	Pruritus			3 (2.6%)		
	Clamminess				4 (4.4%)*	
	Night sweats				3 (3.3%)*	3 (2.7%)*
	Alopecia				2 (2.2%)	
Musculoskeletal	Arthralgia			4 (3.4%)		
	Myalgia				2 (2.2%)	5 (4.5%)
	Pain in limb					3 (2.7%)
Reproductive	Testicular atrophy	6 (5.0%)			4 (4.4%)*	8 (7.2%)*
	Gynecomastia				2 (2.2%)*	4 (3.6%)*
	Testicular pain				2 (2.2%)	
Psychiatric	Decreased libido				3 (3.3%)*	

*Expected pharmacological consequences of testosterone suppression.

In the patient populations studied with ELIGARD® 7.5 mg, a total of 86 hot flashes/sweats adverse events were reported in 70 patients. Of these, 71 events (83%) were mild; 14 (16%) were moderate; 1 (1%) was severe.

In the patient population studied with ELIGARD® 22.5 mg, a total of 84 hot flashes/sweats adverse events were reported in 66 patients. Of these, 73 events (87%) were mild; 11 (13%) were moderate; none were severe.

In the patient population studied with ELIGARD® 30 mg, a total of 75 hot flash adverse events were reported in 66 patients. Of these, 57 events (76%) were mild; 16 (21%) were moderate; 2 (3%) were severe.

In the patient population studied with ELIGARD® 45 mg, a total of 89 hot flash adverse events were reported in 64 patients. Of these, 62 events (70%) were mild; 27 (30%) were moderate; none were severe.

In addition, the following possibly or probably related systemic adverse events were reported by < 2% of the patients treated with ELIGARD® in these clinical studies.

Body system	Adverse event
General	Sweating, insomnia, syncope, rigors, weakness, lethargy
Gastrointestinal	Flatulence, constipation, dyspepsia
Hematologic	Decreased red blood cell count, hematocrit and hemoglobin
Metabolic	Weight gain
Musculoskeletal	Tremor, backache, joint pain, muscle atrophy, limb pain
Nervous	Disturbance of smell and taste, depression, vertigo
Psychiatric	Insomnia, depression, loss of libido*
Renal/urinary	Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine, urinary retention, urinary urgency, incontinence, nocturia, nocturia aggravated
Reproductive/ Urogenital:	Testicular soreness/pain, impotence*, decreased libido*, gynecomastia*, breast soreness/tenderness*, testicular atrophy*, erectile dysfunction, penile disorder*, reduced penis size
Skin	Alopecia, clamminess, night sweats*, sweating increased*
Vascular	Hypertension, hypotension

* Expected pharmacological consequences of testosterone suppression.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

6.2 Postmarketing experience

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 with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some 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.

Convulsions have also been reported in the postmarketing setting.

7. DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD®.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category X. [See '*Contraindications*' section]

ELIGARD® is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with ELIGARD® 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 informed of the potential hazard to the fetus and the potential risk for pregnancy loss.

In non-clinical studies in rats, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects of fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

8.3 Nursing Mothers:

ELIGARD® is not indicated for use in women [*see Indications and Usage (1)*]. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ELIGARD®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ELIGARD® in pediatric patients have not been established.

8.5 Geriatric Use

The majority of the patients (approximately 70%) studied in the clinical trials were age 70 and older.

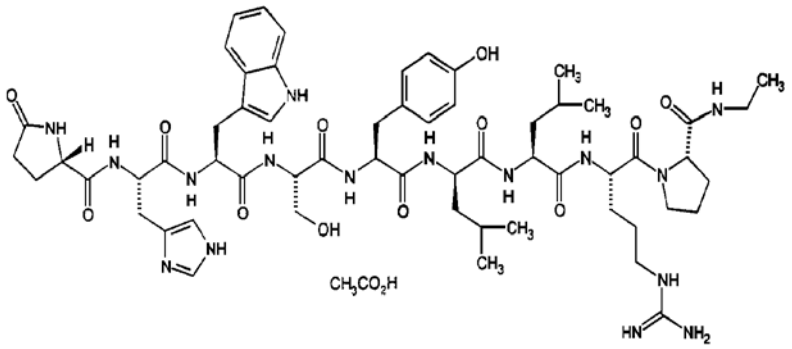
10. OVERDOSAGE

In clinical trials using daily subcutaneous injections of leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

11. DESCRIPTION

ELIGARD® is a sterile polymeric matrix formulation of leuprolide acetate, a GnRH agonist, for subcutaneous injection. It is designed to deliver leuprolide acetate at a controlled rate over a one-, three-, four- or six-month therapeutic period.

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



ELIGARD® is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. ELIGARD® is administered subcutaneously, where it forms a solid drug delivery depot.

One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly (DL-lactide-co-glycolide) (PLGH or PLG) polymer formulation dissolved in a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP).

Refer to Table 5 for the delivery system composition and constituted product formulation for each ELIGARD® product.

Table 5. ELIGARD® Delivery System Composition and Constituted Product Formulation

ELIGARD®		7.5 mg	22.5 mg	30 mg	45 mg
ATRIGEL® Delivery System syringe	Polymer	PLGH	PLG	PLG	PLG
	Polymer description	Copolymer containing carboxyl endgroups	Copolymer with hexanediol	Copolymer with hexanediol	Copolymer with hexanediol
	Polymer DL-lactide to glycolide molar ratio	50:50	75:25	75:25	85:15
Constituted product	Polymer delivered	82.5 mg	158.6 mg	211.5 mg	165 mg
	NMP delivered	160.0 mg	193.9 mg	258.5 mg	165 mg
	Leuprolide acetate delivered	7.5 mg	22.5 mg	30 mg	45 mg
	Approximate Leuprolide free base equivalent	7.0 mg	21 mg	28 mg	42 mg
	Approximate administered formulation weight	250 mg	375 mg	500 mg	375 mg
	Approximate injection volume	0.25 mL	0.375 mL	0.5 mL	0.375 mL

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprolide acetate results in suppression of testicular and ovarian steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold ($\leq$ 50 ng/dL). These decreases occur within two to four weeks after initiation of treatment. Long-term studies have shown that continuation of therapy with leuprolide acetate maintains testosterone below the castrate level for up to seven years.

12.2 Pharmacodynamics

Following the first dose of ELIGARD®, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold (≤ 50 ng/dL) within three weeks for all ELIGARD® concentrations.

Continued monthly treatment with ELIGARD® 7.5 mg maintained castrate testosterone suppression throughout the study. No breakthrough of testosterone concentrations above castrate threshold (> 50 ng/dL) occurred at any time during the study once castrate suppression was achieved (Figure 18).

One patient received less than a full dose of ELIGARD® 22.5 mg at baseline, never suppressed and withdrew from the study at Day 73. Of the 116 patients remaining in the study, 115 (99%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). By Day 35, 116 (100%) had serum testosterone levels below the castrate threshold. Once testosterone suppression was achieved, one patient (< 1%) demonstrated breakthrough (concentrations > 50 ng/dL after achieving castrate levels) following the initial injection; that patient remained below the castrate threshold following the second injection (Figure 19).

One patient withdrew from the ELIGARD® 30 mg study at Day 14. Of the 89 patients remaining in the study, 85 (96%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). By Day 42, 89 (100%) of patients attained castrate testosterone suppression. Once castrate testosterone suppression was achieved, three patients (3%) demonstrated breakthrough (concentrations > 50 ng/dL after achieving castrate levels) (Figure 20).

One patient at Day 1 and another patient at Day 29 were withdrawn from the ELIGARD® 45 mg study. Of the 109 patients remaining in the study, 108 (99.1%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). One patient did not achieve castrate suppression and was withdrawn from the study at Day 85. Once castrate testosterone suppression was achieved, one patient (< 1%) demonstrated breakthrough (concentrations > 50 ng/dL after achieving castrate levels) (Figure 21).

Leuprolide acetate is not active when given orally.

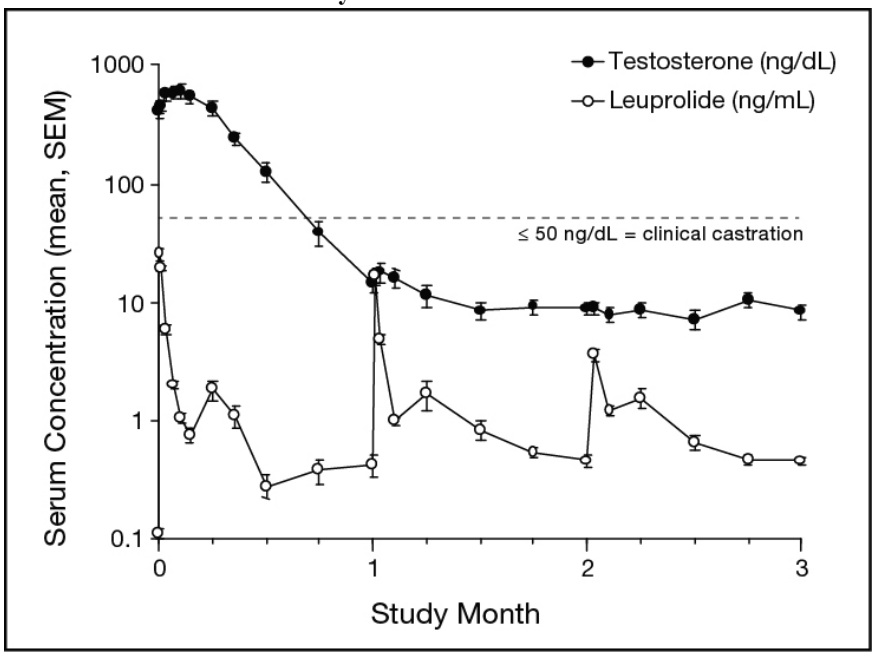
12.3 Pharmacokinetics

Absorption

ELIGARD® 7.5 mg

The pharmacokinetics/pharmacodynamics observed during three once-monthly injections in 20 patients with advanced prostate cancer is shown in Figure 18. Mean serum leuprolide concentrations following the initial injection rose to 25.3 ng/mL (C_{max}) at approximately 5 hours after injection. After the initial increase following each injection, serum concentrations remained relatively constant (0.28 – 2.00 ng/mL).

Figure 18. Pharmacokinetic/Pharmacodynamic Response (N=20) to ELIGARD® 7.5 mg – Patients Dosed Initially and at Months 1 and 2

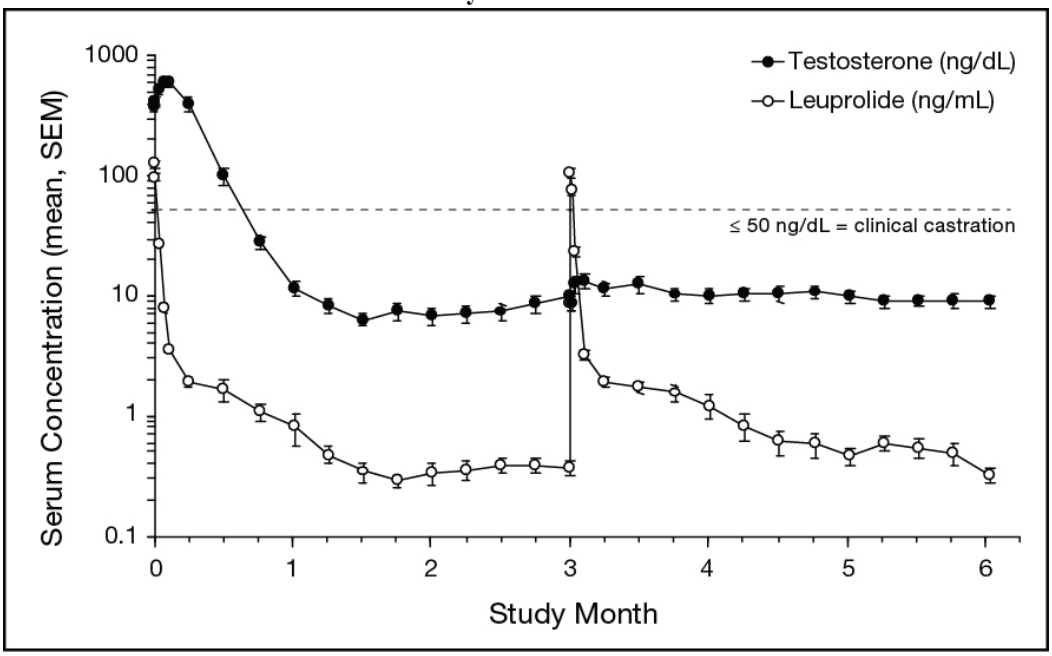


A reduced number of sampling time points resulted in the apparent decrease in C_{max} values with the second and third doses of ELIGARD® 7.5 mg (Figure 18).

ELIGARD® 22.5 mg

The pharmacokinetics/pharmacodynamics observed during two injections every three months (ELIGARD® 22.5 mg) in 22 patients with advanced prostate cancer is shown in Figure 19. Mean serum leuprolide concentrations rose to 127 ng/mL and 107 ng/mL at approximately 5 hours following the initial and second injections, respectively. After the initial increase following each injection, serum concentrations remained relatively constant (0.2 – 2.0 ng/mL).

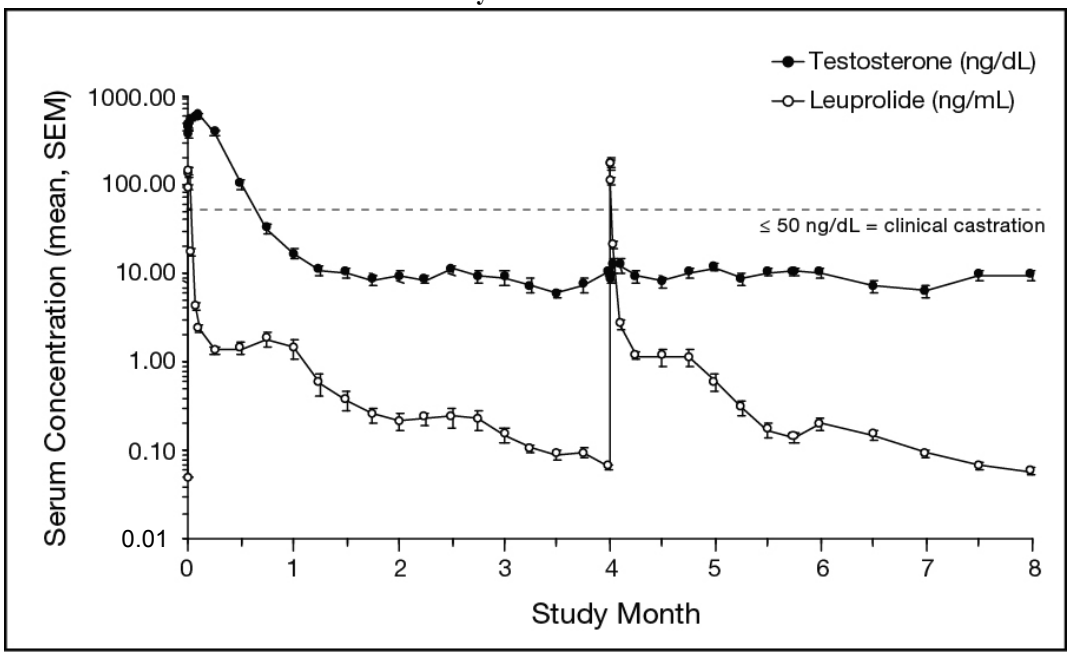
Figure 19. Pharmacokinetic/Pharmacodynamic Response (N=22) to ELIGARD® 22.5 mg – Patients Dosed Initially and at Month 3



ELIGARD® 30 mg

The pharmacokinetics/pharmacodynamics observed during injections administered initially and at four months (ELIGARD® 30 mg) in 24 patients with advanced prostate cancer is shown in Figure 20. Mean serum leuprolide concentrations following the initial injection rose rapidly to 150 ng/mL (C_{max}) at approximately 3.3 hours after injection. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.1 – 1.0 ng/mL).

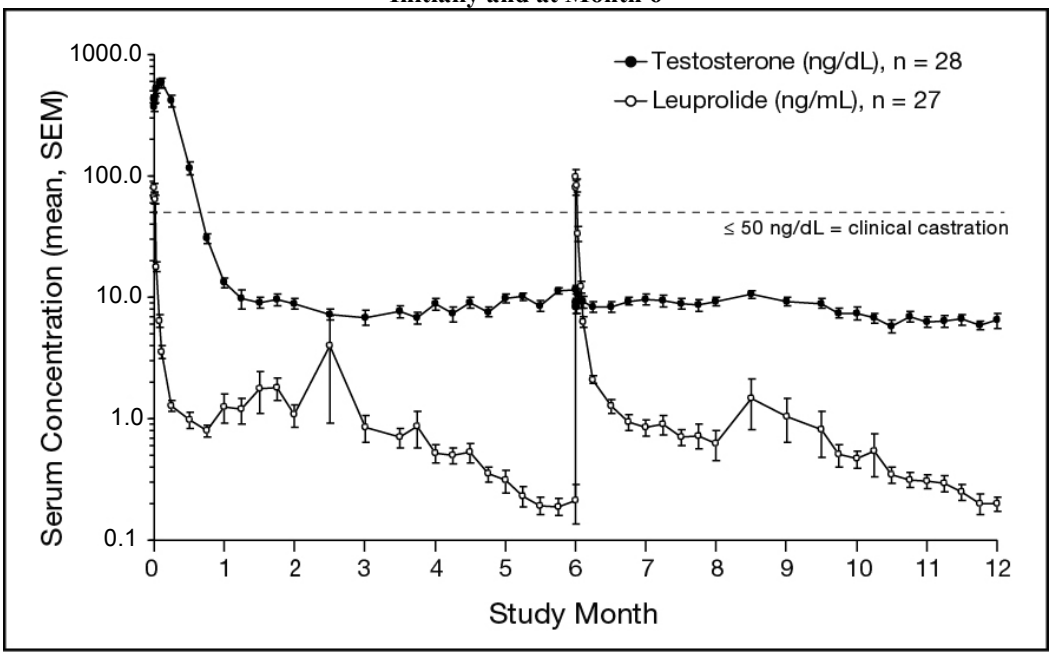
Figure 20. Pharmacokinetic/Pharmacodynamic Response (N=24) to ELIGARD® 30 mg – Patients Dosed Initially and at Month 4



ELIGARD® 45 mg

The pharmacokinetics/pharmacodynamics observed during injections administered initially and at six months (ELIGARD® 45 mg) in 27 patients with advanced prostate cancer is shown in Figure 21. Mean serum leuprolide concentrations rose to 82 ng/mL and 102 ng/mL (C_{max}) at approximately 4.5 hours following the initial and second injections, respectively. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.2 – 2.0 ng/mL).

Figure 21. Pharmacokinetic/Pharmacodynamic Response (N=27) to ELIGARD® 45 mg - Patients Dosed Initially and at Month 6



There was no evidence of significant accumulation during repeated dosing. Non-detectable leuprolide plasma concentrations have been occasionally observed during ELIGARD® administration, but testosterone levels were maintained at castrate levels.

Distribution. The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism. In healthy male volunteers, a 1-mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

No drug metabolism study was conducted with ELIGARD®. Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-1) metabolite.

Excretion. No drug excretion study was conducted with ELIGARD®.

Geriatrics. *[see USE IN SPECIAL POPULATIONS (8.5)]*

Race. In patients studied, mean serum leuprolide concentrations were similar regardless of race. Refer to Table 6 for distribution of study patients by race.

Table 6. Race Characterization of ELIGARD® Study Patients

Race	ELIGARD® 7.5 mg	ELIGARD® 22.5 mg	ELIGARD® 30 mg	ELIGARD® 45 mg
White	26	19	18	17
Black	-	4	4	7
Hispanic	2	2	2	3

Renal and Hepatic Insufficiency. The pharmacokinetics of ELIGARD® in hepatically and renally impaired patients have not been determined.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted with leuprolide acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities. No carcinogenicity studies have been conducted with ELIGARD®.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems and with ELIGARD® 7.5 mg in bacterial systems. These studies provided no evidence of a mutagenic potential.

14. CLINICAL STUDIES

One open-label, multicenter study was conducted with each ELIGARD® formulation (7.5 mg, 22.5 mg, 30 mg, and 45 mg) in patients with Jewett stage A though D prostate cancer who were treated with at least a single injection of study drug (Table 7). These studies evaluated the achievement and maintenance of castrate serum testosterone suppression over the duration of therapy (Figures 22-25).

During the AGL9904 study using ELIGARD® 7.5 mg, once testosterone suppression was achieved, no patients (0%) demonstrated breakthrough (concentration >50 ng/dL) at any time in the study.

During the AGL9909 study using ELIGARD® 22.5 mg, once testosterone suppression was achieved, only one patient (< 1%) demonstrated breakthrough following the initial injection; that patient remained below the castrate threshold following the second injection.

During the AGL0001 study using ELIGARD® 30 mg, once testosterone suppression was achieved, three patients (3%) demonstrated breakthrough. In the first of these patients, a single serum testosterone concentration of 53 ng/dL was reported on the day after the second injection. In this patient, castrate suppression was reported for all other time points. In the second patient, a serum testosterone concentration of 66 ng/dL was reported immediately prior to the second injection. This rose to a maximum concentration of 147 ng/dL on the second day after the second injection. In this patient, castrate suppression was again reached on the seventh day after the second injection and was maintained thereafter. In the final patient, serum testosterone concentrations > 50 ng/dL were reported at 2 and at 8 hours after the second injection. Serum testosterone concentration rose to a maximum of 110 ng/dL on the third day after the second injection. In this patient, castrate suppression was again reached eighteen days after the second injection and was maintained until the final day of the study, when a single serum testosterone concentration of 55 ng/dL was reported.

During the AGL0205 study using ELIGARD® 45 mg, once testosterone suppression was achieved, one patient (<1%) demonstrated breakthrough. This patient reached castrate suppression at Day 21 and remained suppressed until Day 308 when his testosterone level rose to 112 ng/dL. At Month 12 (Day 336), his testosterone was 210 ng/dL.

Table 7. Summary of ELIGARD® Clinical Studies

ELIGARD®		7.5 mg	22.5 mg	30 mg	45 mg
Study number		AGL9904	AGL9909	AGL0001	AGL0205
Total number of patients		120 (117 completed)	117[2] (111 completed[3])	90 (82 completed[4])	111 (103 completed[5])
Jewett stages	Stage A	-	2	2	5
	Stage B	-	19	38	43
	Stage C	89	60	16	19
	Stage D	31	36	34	44
Treatment		6 monthly injections	1 injection (4 patients)	1 injection (5 patients)	1 injection (5 patients)
			2 injections, one every three months (113 patients)	2 injections, one every four months (85 patients)	2 injections, one every six months (106 patients)
Duration of therapy		6 months	6 months	8 months	12 months
Mean testosterone concentration (ng/dL)	Baseline	361.3	367.1	385.5	367.7
	Day 2	574.6 (Day 3)	588.0	610.0	588.6
	Day 14	Below Baseline (Day 10)	Below Baseline	Below Baseline	Below Baseline
	Day 28	21.8	27.7 (Day 21)	17.2	16.7
	Conclusion	6.1	10.1	12.4	12.6
Number of patients below castrate threshold (≤ 50 ng/dL)	Day 28	112 of 119 (94.1%)	115 of 116 (99%)	85 of 89 (96%)	108 of 109 (99.1%)
	Day 35	-	116 (100%)	-	-
	Day 42	119 (100%)	-	89 (100%)	-
	Conclusion	117[1] (100%)	111 (100%)	81 (99%)	102 (99%)

1. Two patients withdrew for reasons unrelated to drug.
2. One patient received less than a full dose at Baseline, never suppressed, and was withdrawn at Day 73 and given an alternate treatment.
3. All non-evaluable patients who attained castration by Day 28 maintained castration at each time point up to and including the time of withdrawal.
4. One patient withdrew on Day 14. All 7 non-evaluable patients who had achieved castration by Day 28 maintained castration at each time point, up to and including the time of withdrawal.
5. Two patients were withdrawn prior to the Month 1 blood draw. One patient did not achieve castration and was withdrawn on Day 85. All 5 non-evaluable patients who attained castration by Day 28, maintained castration at each time point up to and including the time of withdrawal.

Figure 22. ELIGARD® 7.5 mg Mean Serum Testosterone Concentrations (n=117)

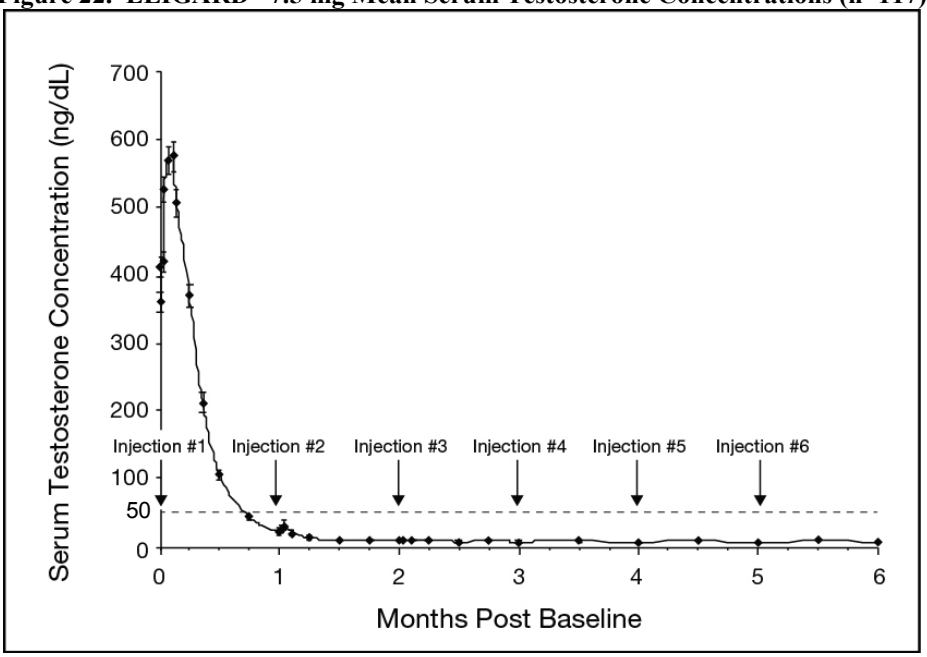


Figure 23. ELIGARD® 22.5 mg Mean Serum Testosterone Concentrations (n=111)

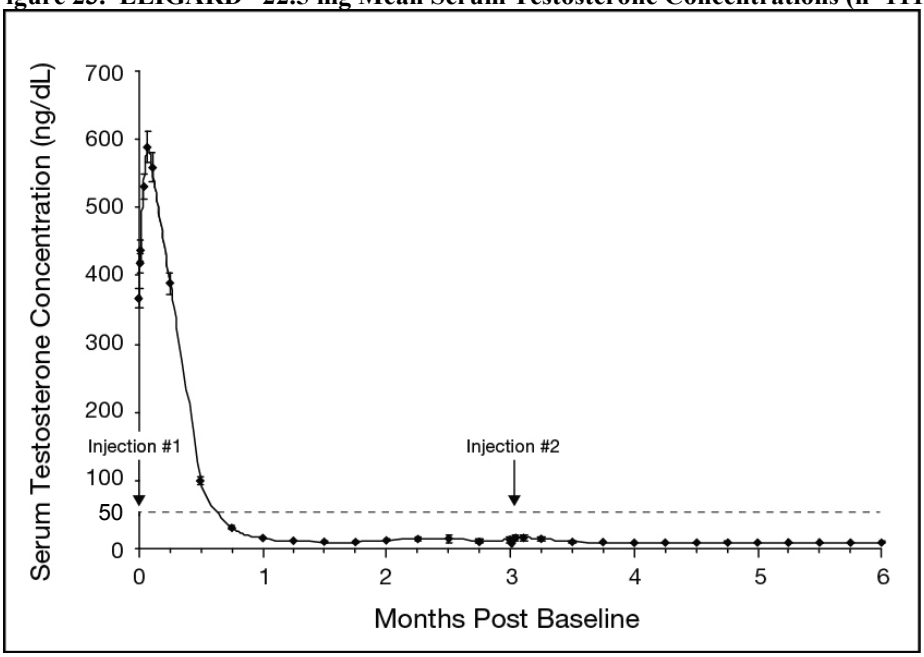


Figure 24. ELIGARD® 30 mg Mean Serum Testosterone Concentrations (n=90)

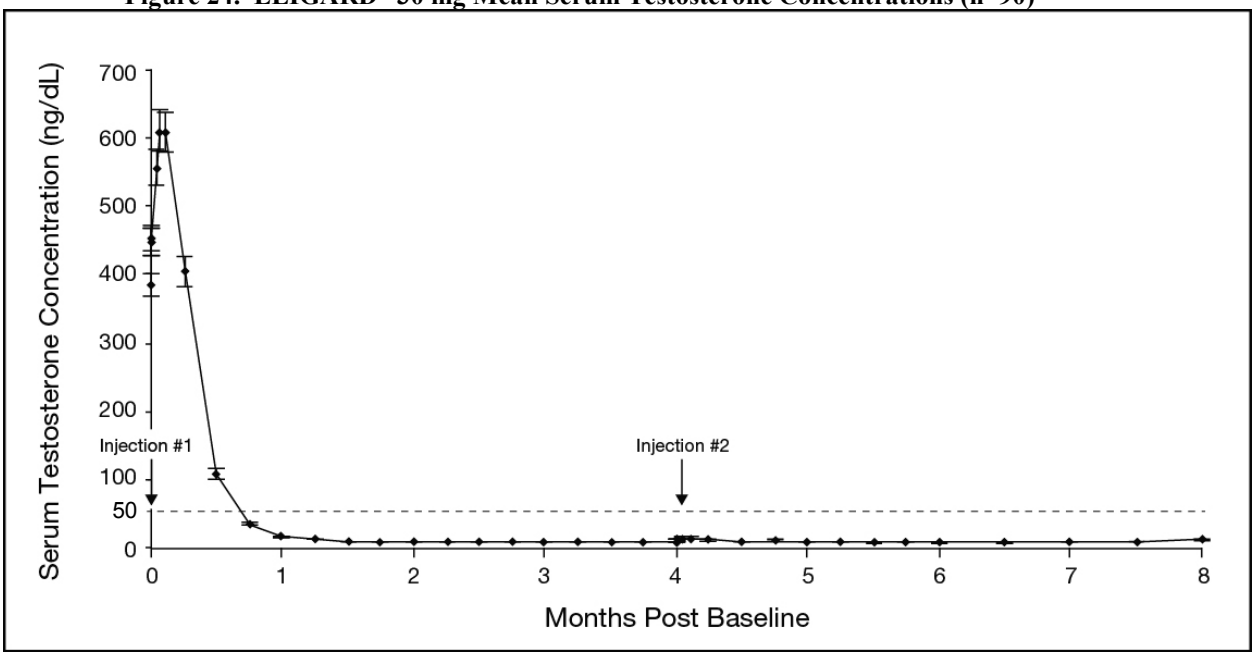
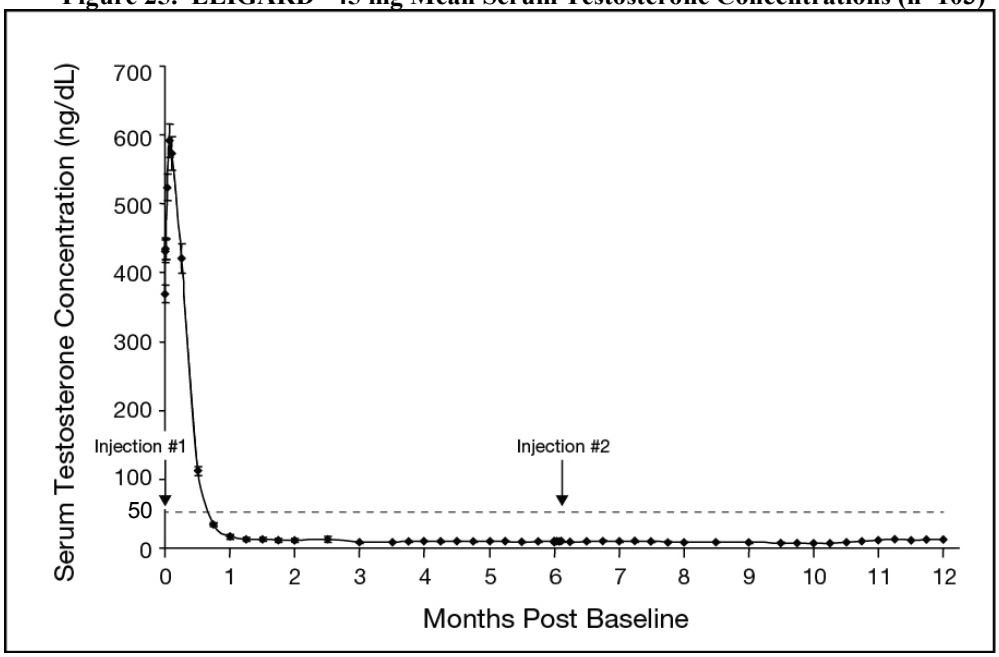


Figure 25. ELIGARD® 45 mg Mean Serum Testosterone Concentrations (n=103)



Serum PSA decreased in all patients in all studies whose Baseline values were elevated above the normal limit. Refer to Table 8 for a summary of the effectiveness of ELIGARD® in reducing serum PSA values.

Table 8. Effect of ELIGARD® on Patient Serum PSA Values

ELIGARD®	7.5 mg	22.5 mg	30 mg	45 mg
Mean PSA reduction at study conclusion	94%	98%	86%	97%
Patients with normal PSA at study conclusion*	94%	91%	93%	95%

*Among patients who presented with elevated levels at Baseline

Other secondary efficacy endpoints evaluated included WHO performance status, bone pain, urinary pain and urinary signs and symptoms. Refer to Table 9 for a summary of these endpoints.

Table 9. Secondary Efficacy Endpoints

ELIGARD®		7.5 mg	22.5 mg	30 mg	45 mg
Baseline	WHO Status = 0[1]	88%	94%	90%	90%
	WHO Status = 1[2]	11%	6%	10%	7%
	WHO Status = 2[3]				3%
	Mean bone pain[4] (range)	1.22 (1-9)	1.20 (1-9)	1.20 (1-7)	1.38 (1-7)
	Mean urinary pain (range)	1.12 (1-5)	1.02 (1-2)	1.01 (1-2)	1.22 (1-8)
	Mean urinary signs and symptoms (range)	Low	1.09 (1-4)	Low	Low
	Number of patients with prostate abnormalities	102 (85%)	96 (82%)	66 (73%)	89 (80%)
		Month 6	**Month 6**	**Month 8**	**Month 12**
Follow-up	WHO status = 0	Unchanged	96%	87%	94%
	WHO status = 1	Unchanged	4%	12%	5%
	WHO status = 2			1%	1%
	Mean bone pain (range)	1.26 (1-7)	1.22 (1-5)	1.19 (1-8)	1.31 (1-8)
	Mean urinary pain (range)	1.07 (1-8)	1.10 (1-8)	1.00 (1-1)	1.07 (1-5)
	Mean urinary signs and symptoms (range)	Modestly decreased	1.18 (1-7)	Modestly decreased	Modestly decreased
	Number of patients with prostate abnormalities	77 (64%)	76 (65%)	54 (60%)	60 (58%)

1. WHO status = 0 classified as “fully active.”
2. WHO status = 1 classified as “restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.”
3. WHO status = 2 classified as “ambulatory but unable to carry out work activities.”
4. Pain score scale: 1 (no pain) to 10 (worst pain possible).

15. REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

ELIGARD® is available in a single use kit of a two syringe-mixing system with a sterile needle in the following strengths:

ELIGARD® 7.5 mg – NDC 62935-752-75
ELIGARD® 22.5 mg – NDC 62935-222-05
ELIGARD® 30 mg – NDC 62935-302-30
ELIGARD® 45 mg – NDC 62935-452-45

ELIGARD® is available in a single use kit of a two syringe-mixing system with a sterile safety needle in the following strengths:

ELIGARD® 7.5 mg – NDC 62935-753-75
ELIGARD® 22.5 mg – NDC 62935-223-05
ELIGARD® 30 mg – NDC 62935-303-30
ELIGARD® 45 mg – NDC 62935-453-45

16.2 Storage:

Store at 2 - 8 °C (35.6 – 46.4 °F)

Once outside the refrigerator this product may be stored in its original packaging at room temperature 15 – 30 °C (59 – 86 °F) for up to eight weeks prior to mixing and administration.

17. PATIENT COUNSELING INFORMATION

As with other GnRH agonists, patients may experience hot flashes. During the first few weeks of treatment, patients may also experience increased bone pain, increased difficulty in urinating, and the onset or aggravation of weakness or paralysis. Patients should notify their doctor if they develop new or worsened symptoms after beginning ELIGARD® treatment. Patients should be told about the injection site related adverse reactions, such as transient burning/stinging, pain, bruising, and redness. These injection site reactions are usually mild and reversible. If they do not resolve, patients should tell their doctor. If the patient experiences an allergic reaction, they should contact their doctor immediately.

Rx only

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Fort Collins, CO 80526

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