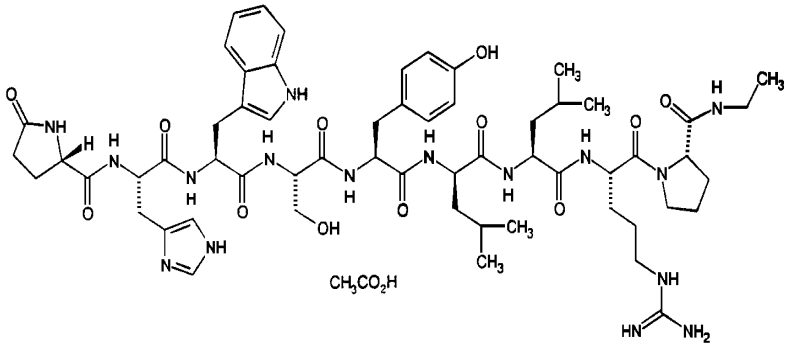
ELIGARD™ 22.5 mg (leuprolide acetate for injectable suspension)

DESCRIPTION

ELIGARD™ 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month therapeutic period.

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) 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 with the following structural formula:



ELIGARD™ 22.5 mg 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™ 22.5 mg is administered once every three months 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) (PLG) polymer formulation dissolved in a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 22.5 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD™ 22.5 mg delivers 22.5 mg of leuprolide acetate (equivalent to approximately 21 mg leuprolide free base) dissolved in 193.9 mg *N*-methyl-2-pyrrolidone and 158.6 mg poly(DL-lactide-co-glycolide). The approximate weight of the administered formulation is 375 mg.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH 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 the levels of 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 (≤ 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.

PHARMACODYNAMICS

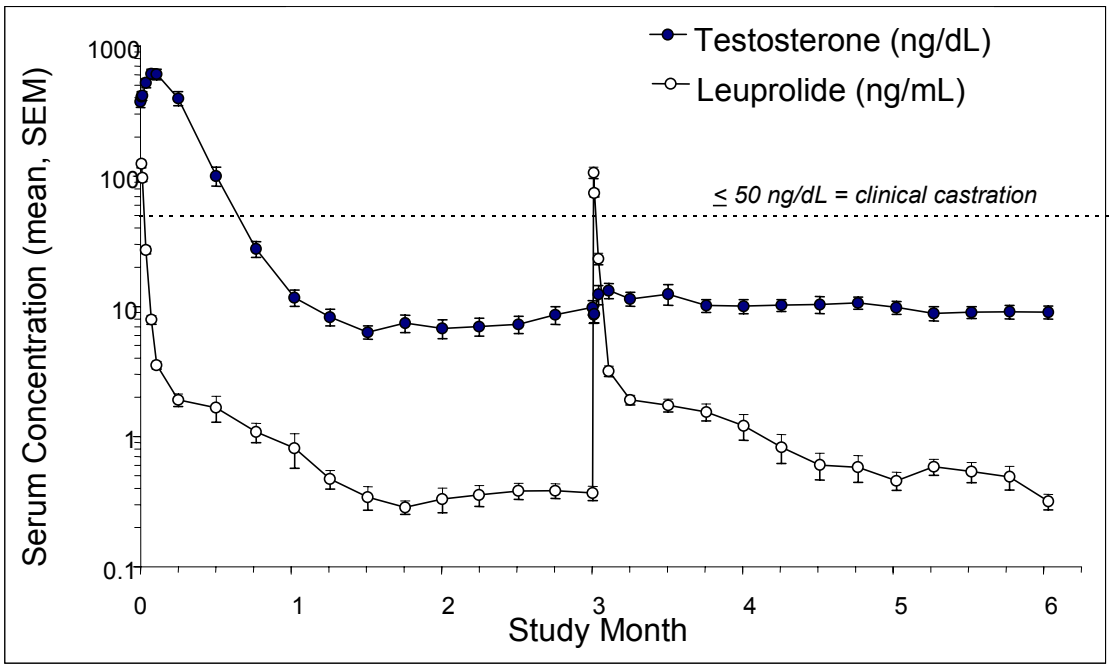
Following the first dose of ELIGARD™ 22.5 mg, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold (≤ 50 ng/dL) within three weeks (Figure 1). Continued treatment maintained castrate testosterone suppression throughout the study. No breakthrough of testosterone concentrations above castrate threshold (>50 ng/dL) occurred at any time during the study once castrate suppression was achieved in subset of 22 patients.

Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption: The pharmacokinetics/pharmacodynamics observed during two injections every three months (ELIGARD™ 22.5 mg) in 22 patients with advanced carcinoma of the prostate is shown in Figure 1. 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 leuprolide concentrations remained relatively constant (0.2 – 2.0 ng/mL). There was no evidence of significant accumulation during repeated dosing. Nondetectable leuprolide plasma concentrations have been observed during chronic ELIGARD™ 22.5 mg administration, but testosterone levels were maintained at castrate levels.

Figure 1 – Pharmacokinetic/Pharmacodynamic Response (n= 22) to ELIGARD™ 22.5 mg Patients Dosed Initially and at Month 3.



Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L.[1] *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.[1]

No drug metabolism study was conducted with ELIGARD™ 22.5 mg. 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™ 22.5 mg.

Special Populations:
Geriatrics: The majority (71%) of the 117 patients studied in the clinical trial were age 70 and older.

Pediatrics: The safety and effectiveness of ELIGARD™ 22.5 mg in pediatric patients have not been established (see **CONTRAINDICATIONS**).

Race: In patients studied (19 White, 4 Black, 2 Hispanic), mean serum leuprolide concentrations were similar.

Renal and Hepatic Insufficiency: The pharmacokinetics of ELIGARD™ 22.5 mg in hepatically and renally impaired patients have not been determined**.**

Drug-Drug Interactions: No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD™ 22.5 mg.

CLINICAL STUDIES

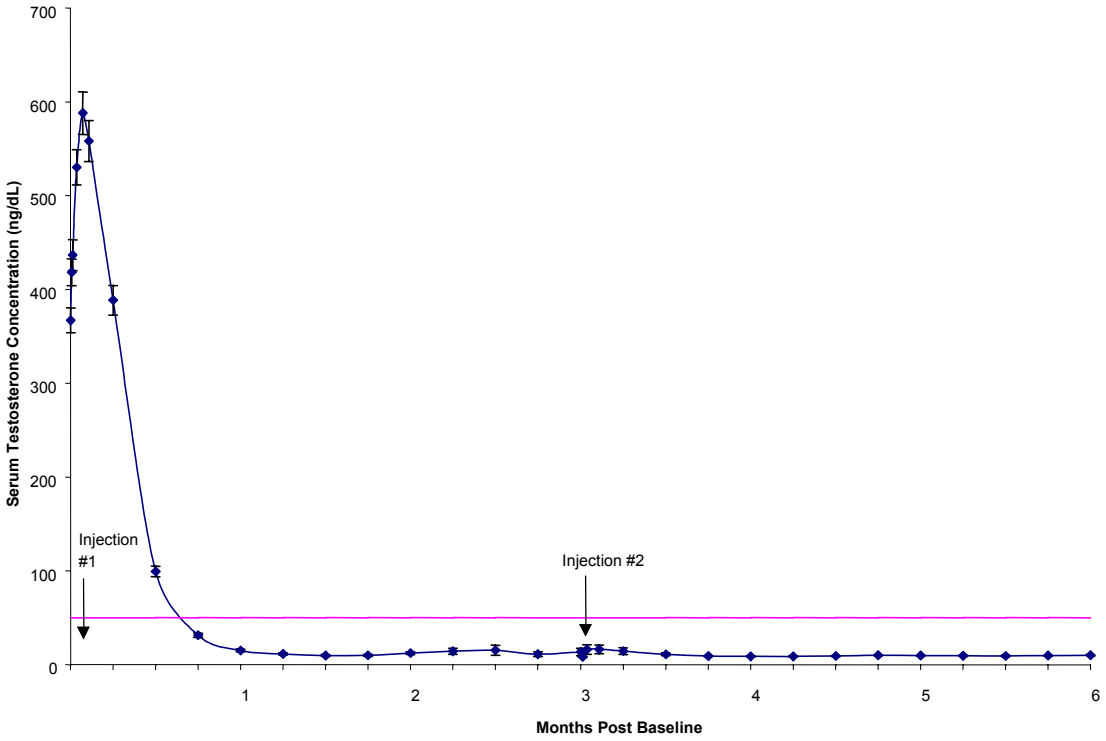
In one open-label, multicenter study (AGL9909), 117 patients with advanced prostate cancer were treated with at least a single injection of study drug. Of these, 113 patients received a total of two injections of ELIGARD™ 22.5 mg, given once every three months. Two patients had stage A disease, 19 patients had stage B, 60 patients had stage C, and 36 patients had stage D. This study evaluated the achievement and maintenance of castrate serum testosterone suppression over six months of therapy. A total of 111 patients completed the study.

The mean testosterone concentration increased from 367.1 ng/dL at Baseline to 588.0 ng/dL at Day 2 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below Baseline by Day 14 and was 27.7 ng/dL on Day 21. At the conclusion of the study (Month 6), mean testosterone concentration was 10.1 ng/dL (Figure 2).

Of the original 117 patients, one received less than a full dose of ELIGARD™ 22.5 mg at Baseline, never suppressed, and was withdrawn at Day 73 and given an alternate treatment. In the remaining 116 patients who did receive the full dose at Baseline, serum testosterone was suppressed to below the castrate threshold (≤ 50 ng/dL) by Day 28 (Week 4) in 115 of 116 patients (99%). By Day 35, all 116 patients (100%) who received a full dose at Baseline attained the castrate threshold. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, only one patient (<1%) demonstrated breakthrough (concentrations above 50 ng/dL) following the initial injection; that patient remained below the castrate threshold following the second injection. All 111 evaluable patients in the study at Month 6 had testosterone concentrations of $\underline{\leq}$ 50 ng/dL.

All non-evaluable patients who attained castration by Day 28 maintained castration at each timepoint up to and including the time of withdrawal.

Figure 2. ELIGARD™ 22.5 mg Mean Serum Testosterone Concentrations (n = 111)



Serum PSA decreased in all patients whose Baseline values were elevated above the normal limit. Mean values were reduced 98% from Baseline to Month 6. At Month 6, PSA levels had decreased to within normal limits in 91% of 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. At Baseline, 94% of patients were classified as "fully active" by the WHO performance status scale (Status=0) and 6% as "restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature" (Status=1). At Month 6, these percentages were changed to 96% (Status=0) and 4% (Status=1). At Baseline, patients experienced little bone pain, with a mean score of 1.20 (range 1-9) on a scale of 1 (no pain) to 10 (worst pain possible). At Month 6, the mean bone pain score was essentially unchanged at 1.22 (range 1-5). Urinary pain, scored on the same scale, was similarly low, with a mean of 1.02 at Baseline (range 1-2) and 1.10 at Month 6 (range 1-8). Urinary signs and symptoms demonstrated a mean score of 1.09 at Baseline (range 1-4) and increase to 1.18 at Month 6 (range 1-7). In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 96 (82%) at Screening to 76 (65%) at Month 6.

INDICATIONS AND USAGE

ELIGARD™ 22.5 mg is indicated for the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

1. ELIGARD™ 22.5 mg is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD™ 22.5 mg. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.[2]

2. ELIGARD™ 22.5 mg is contraindicated in women and in pediatric patients and was not studied in women or children. Moreover, leuprolide acetate can cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

WARNINGS

ELIGARD™ 22.5 mg, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week 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. Isolated 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 LH-RH agonists. (see **PRECAUTIONS**)

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

PRECAUTIONS

General: Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy. (see **WARNINGS** section)

Laboratory tests: Response to ELIGARD™ 22.5 mg should be monitored by measuring serum concentrations of testosterone and prostate specific antigen periodically.

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 week. Castrate levels were generally reached within two to four weeks and once achieved were maintained for the duration of treatment.

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 Interactions: **See PHARMACOKINETICS**

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.

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 a 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™ 22.5 mg.

Mutagenicity studies were 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.

Pregnancy, Teratogenic Effects: Pregnancy category X. (See **CONTRAINDICATIONS**)

Pediatric Use: ELIGARD™ 22.5 mg is contraindicated in pediatric patients and was not studied in children (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The safety of ELIGARD™ 22.5 mg was evaluated in 117 patients with advanced prostate cancer. ELIGARD™ 22.5 mg, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first 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**)

In Study AGL9909, 117 patients were dosed with ELIGARD™ 22.5 mg every three months for up to six months and injection sites were closely monitored. In all, 230 injections of ELIGARD™ 22.5 mg were administered. Transient burning/stinging was reported following 50 injections (21.7%), with the majority (86%) of these events reported as mild. Pain was reported following 3.5% of study injections (6.0% of patients) and was generally reported as brief in duration and mild in intensity.

Erythema was reported following 2 injections (0.9% of study injections, 1.7% of patients). One of the reports characterized the erythema as mild and resolved within 7 days. The other was moderate and resolved within 15 days. Neither patient experienced erythema at multiple injections. Mild bruising was reported following 4 injections (1.7% of study injections, 3.4% of patients). Mild pruritis was reported following 1 injection (0.4% of study injections, 0.9% of patients).

These localized adverse events were nonrecurrent 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 of up to six months of treatment with ELIGARD™ 22.5 mg, and were reported in ≥ 2% of patients (Table 1). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

Table 1: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥2% of Patients (n=117) Treated with ELIGARD™ 22.5 mg for up to Six Months; Study AGL 9909

Body System	Adverse Event	Number	Percent
Vascular Disorders	Hot flashes/sweats*	66	56.4%
Body as a Whole	Fatigue	7	6.0%
Genitourinary	Urinary frequency	3	2.6%
Gastrointestinal	Nausea	4	3.4%
Skin and Subcutaneous Tissue	Pruritis	3	2.6%
Musculoskeletal	Arthralgia	4	3.4%

In addition, the following possibly or probably related systemic adverse events were reported by <2% of the patients using ELIGARD™ 22.5 mg in the clinical study.

Gastrointestinal: Dyspepsia
General: Rigors, weakness, lethargy
Renal: Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine and urinary retention
Reproductive: Breast tenderness*, testicular atrophy*, testicular pain, gynecomastia*, impotence*

Skin: Clamminess, night sweats*, sweating increased*
Vascular: Hypertension, hypotension

* Expected pharmacological consequence of testosterone suppression. In the patient population studied, a total of 84 hot flash/sweats events were reported in 66 patients. Of these, 73 events (87%) were described as mild; 11 (13%) as moderate; none were severe.

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 an LH-RH agonist analog.[3] It can be anticipated that long periods of medical castration in men will have effects on bone density.

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.

DOSAGE AND ADMINISTRATION

The recommended dose of ELIGARD™ 22.5 mg is one injection every three months. The injection delivers 22.5 of mg leuprolide acetate, incorporated in a polymer formulation . It is administered subcutaneously and provides continuous release of leuprolide for three months.

Once mixed, ELIGARD™ 22.5 mg should be discarded if not administered within 30 minutes.

As with other drugs administered by subcutaneous injection, the injection site should vary periodically.

Mixing Procedure

IMPORTANT: Allow the product to reach room temperature before using. **Once mixed, the product must be administered within 30 minutes.**

Follow the instructions as directed to ensure proper preparation of ELIGARD™ 22.5 mg prior to administration:

ELIGARD™ 22.5 mg is packaged in a pouch that contains two smaller pouches (Figure 3), a needle cartridge and a desiccant pack (Figure 4). Syringe A pouch contains the sterile Syringe A pre-filled with the ATRIGEL® polymer system and a long white replacement plunger rod (Figure 5). Syringe B pouch contains the sterile Syringe B pre-filled with leuprolide acetate powder (Figure 6).

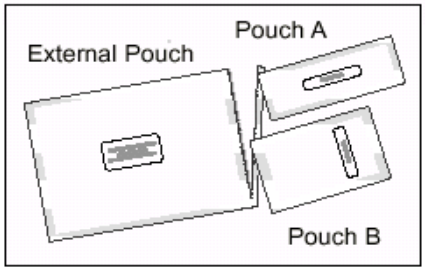
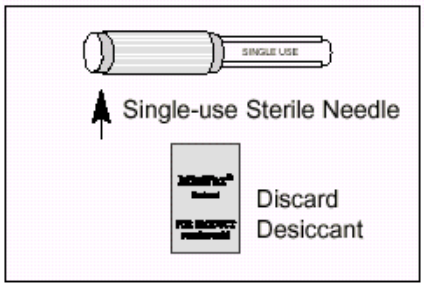


Figure 3



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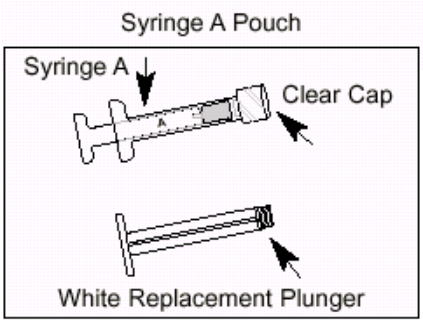


Figure 5

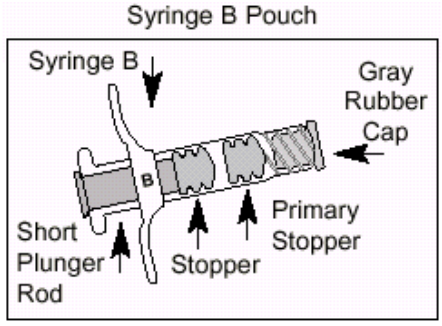
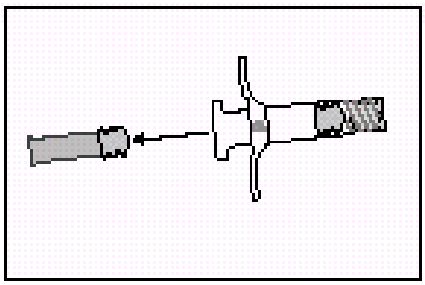


Figure 6

1. On a clean field, open all of the pouches and remove the contents. Discard the desiccant pack.



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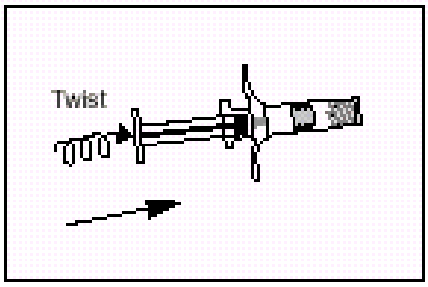

Figure 8

2. Pull out the blue-tipped short plunger rod and attached stopper from Syringe B and discard (Figure 7). Gently insert the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B by twisting it in place (Figure 8).

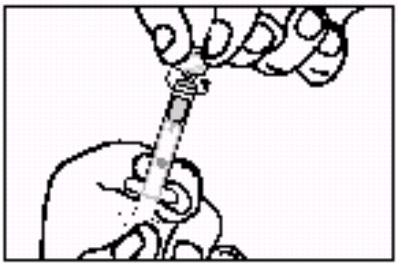

Figure 9

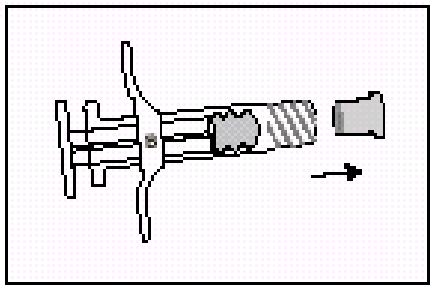

Figure 10

3. Unscrew the clear cap from Syringe A (Figure 9). Remove the gray rubber cap from Syringe B (Figure 10).

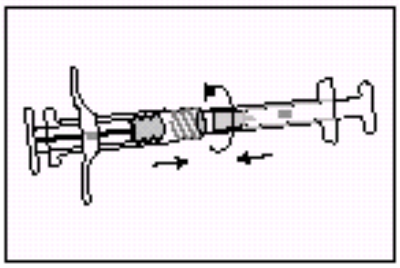

Figure 11

4. Join the two syringes together by pushing in and twisting until secure (Figure 11).

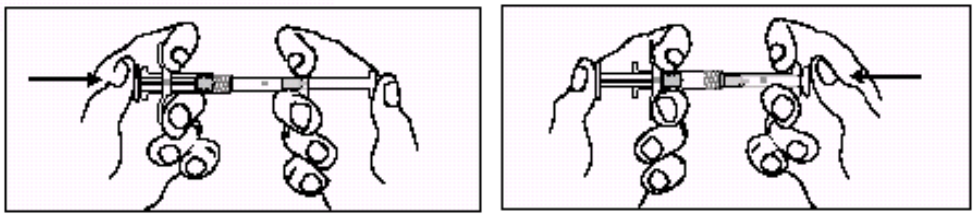

Figure 12

5. Thoroughly mix the product by pushing the contents of both syringes back and forth between syringes (approximately 45 seconds) to obtain a uniform suspension (Figure 12). When thoroughly mixed, the suspension will appear a light tan to tan color. **Please note: Product must be mixed as described; shaking will not provide adequate mixing of the product**.

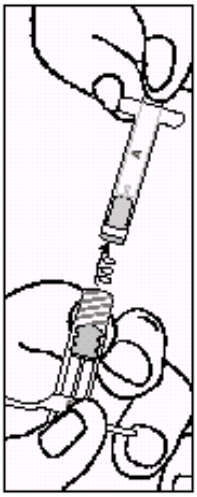

Figure 13

6. 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. Uncouple Syringe A while continuing to push down on the Syringe A plunger (Figure 13). **Please note**: **Small air bubbles will remain in the formulation – this is acceptable.**

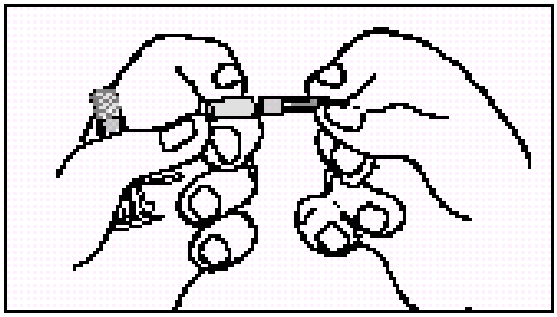

Figure 14

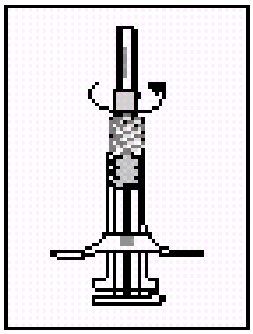

Figure 15

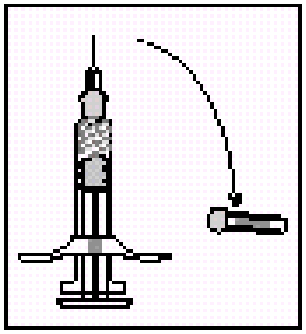

Figure 16

7. Hold Syringe B upright. Remove the pink cap on the bottom of the sterile needle cartridge by twisting it (Figure 14). Attach the needle cartridge to the end of Syringe B (Figure 15) by pushing in and turning the needle until it is firmly seated. Do not twist the needle onto the syringe until it is stripped. Pull off the clear needle cartridge cover prior to administration (Figure 16). After administration discard all components safely in an appropriate biohazard container.

HOW SUPPLIED

ELIGARD™ 22.5 mg is available in a single use kit. The kit consists of a two-syringe mixing system, a 20-gauge half-inch needle, a silicone 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. When constituted, ELIGARD™ 22.5 mg is administered as a single dose.

(NDC xxxxx-xxx-x)

Rx only

Store at 2 - 8 °C (35.6 – 46.4 °F)

Atrix Laboratories, Inc.
Fort Collins, CO 80525

04XXXX, Rev 0 9/01

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[1] Sennello LT et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. J Pharm Sci 1986; 75(2): 158-160.

2 MacLeod TL et. al. Anaphylactic reaction to synthetic luteinizing hormone releasing hormone. Fertil Steril 1987 Sept; 48(3): 500-502.

3 Hatano T et. al. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJU International 2000 86: 449-452.

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Daniel A. Shames
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