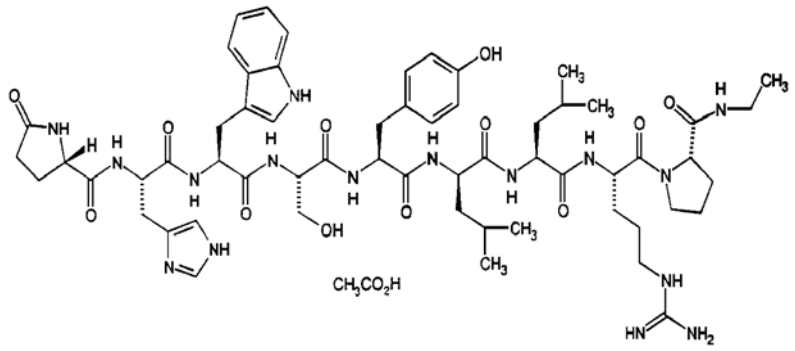
ELIGARD® 45 mg

(leuprolide acetate for injectable suspension)

DESCRIPTION

ELIGARD® 45 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 45 mg of leuprolide acetate at a controlled rate over a six-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® 45 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® 45 mg is administered once every six 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 an 85:15 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 45 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD® 45 mg delivers 45 mg of leuprolide acetate (equivalent to approximately 42 mg leuprolide free base) dissolved in 165 mg *N*-methyl-2-pyrrolidone and 165 mg poly(DL-lactide-co-glycolide). The approximate weight of the administered formulation is 375 mg. The approximate injection volume is 0.375 mL.

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 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.

PHARMACODYNAMICS

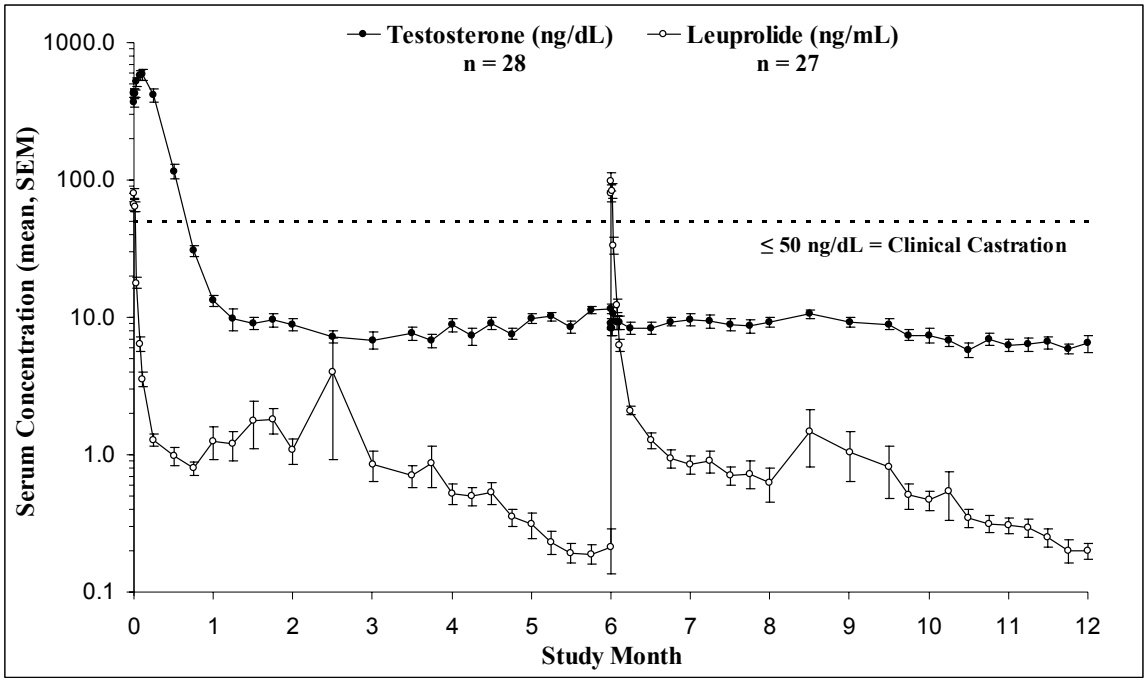
Following the first dose of ELIGARD® 45 mg, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold ($\leq$ 50 ng/dL) within three weeks (Figure 1). One patient at Day 1 and another patient at Day 29 were withdrawn from the study before the Month 1 blood draw. 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 above 50 ng/dL after achieving castrate levels).

Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption: The pharmacokinetics/pharmacodynamics observed during injections administered initially and at six months (ELIGARD® 45 mg) in 27 patients with advanced carcinoma of the prostate is shown in Figure 1. 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). There was no evidence of significant accumulation during repeated dosing. Nondetectable leuprolide plasma concentrations have been occasionally observed during ELIGARD® 45 mg administration, but testosterone levels were maintained at castrate levels.

Figure 1 Pharmacokinetic/Pharmacodynamic Response (N = 27) to ELIGARD® 45 mg - Patients Dosed Initially and at Month 6



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 three hours based on a two compartment model.[1]

No drug metabolism study was conducted with ELIGARD® 45 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® 45 mg.

Special Populations:

Geriatrics: The majority (72%) of the 111 patients studied in the clinical trial were age 70 and older.

Pediatrics: The safety and effectiveness of ELIGARD® 45 mg in pediatric patients have not been established (see **CONTRAINDICATIONS**).

Race: In patients studied (17 White, 7 Black, 3 Hispanic), mean serum leuprolide concentrations were similar.

Renal and Hepatic Insufficiency: The pharmacokinetics of ELIGARD® 45 mg in hepatically and renally impaired patients have not been determined.

Drug-Drug Interactions: No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD® 45 mg.

CLINICAL STUDIES

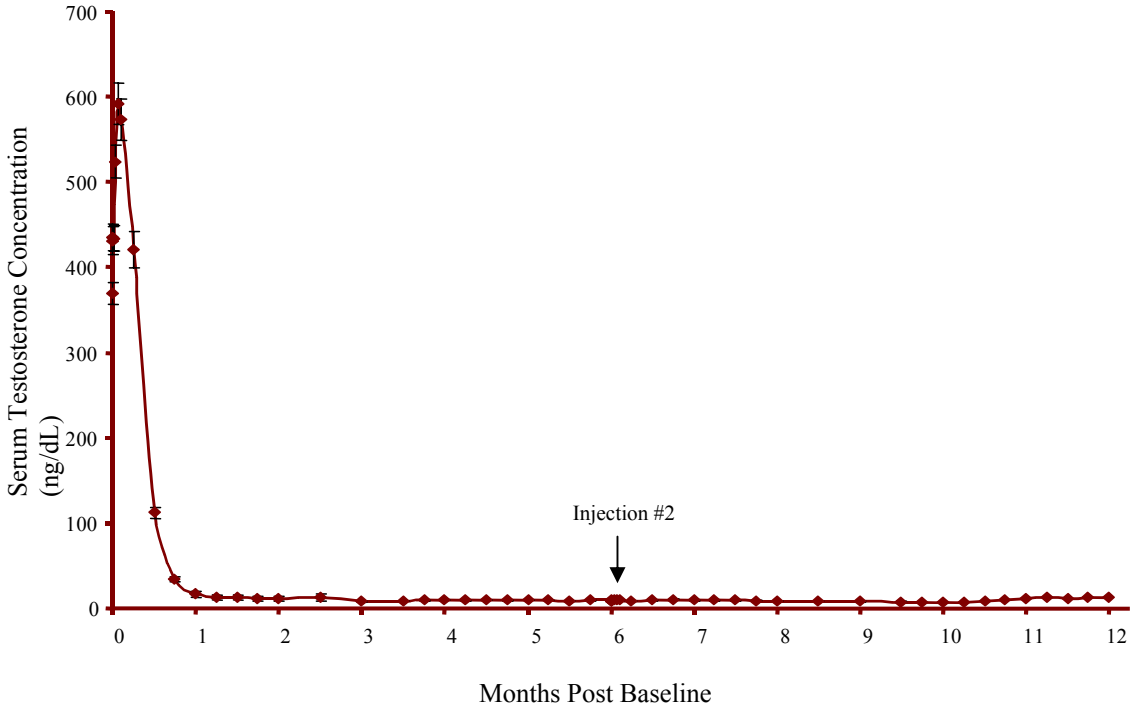
In one open-label, multicenter study (AGL0205), 111 patients with advanced prostate cancer were treated with at least a single injection of study drug. Of these, 106 patients received a total of two injections of ELIGARD® 45 mg given once every six months. Five patients had Jewett stage A disease, 43 had stage B disease, 19 had stage C disease and 44 patients had stage D disease. This study evaluated the achievement and maintenance of castrate serum testosterone suppression over 12 months of therapy. A total of 103 patients completed the study.

The mean serum testosterone concentration increased from 367.7 ng/dL at Baseline to 588.6 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 16.7 ng/dL on Day 28. At the conclusion of the study (Month 12), mean serum testosterone concentration was 12.6 ng/dL (Figure 2).

Of the original 111 patients, two were withdrawn from the study prior to the Month 1 blood draw. Serum testosterone was suppressed to below the castrate threshold ($\leq$ 50 ng/dL) by Day 28 in 108 of 109 (99.1%) patients remaining in the study. One patient (< 1%) did not achieve castrate suppression and was withdrawn from the study on Day 85. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, one patient (< 1%) demonstrated breakthrough (concentration above 50 ng/dL) during the study. 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. Of 103 evaluable patients in the study at Month 12, 102 had testosterone concentrations of $\leq$ 50 ng/dL.

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

Figure 2 ELIGARD® 45 mg Mean Serum Testosterone Concentrations (n = 103)



Serum PSA decreased in all patients whose Baseline values were elevated above the normal limit. Individual mean values were reduced an average of 97% from Baseline to Month 12. At Month 12, PSA levels had decreased to within normal limits in 95% 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, 90% of patients were classified as "fully active" by the WHO performance status scale (Status=0), 7% as "restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature" (Status=1), and 3% as "ambulatory but unable to carry out work activities" (Status = 2). At Month 12, the percentage of fully active men increased slightly to 94%, the percentage of men classified as restricted decreased slightly to 5%, and one patient (1%) remained classified as unable to carry out work activities. At Baseline, patients experienced little bone pain, with a mean score of 1.38 (range 1-7) on a scale of 1 (no pain) to 10 (worst pain possible). At Month 12, the mean bone pain score was essentially unchanged at 1.31 (range 1-8). Urinary pain, scored on the same scale, was similarly low, with a mean of 1.22 at Baseline (range 1-8) and was essentially unchanged at Month 12, with a mean score of 1.07 (range 1-5). Urinary signs and symptoms were similarly low at Baseline and decreased modestly at Month 12. In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 89 (80%) at Screening to 60 (58%) at Month 12.

INDICATIONS AND USAGE

ELIGARD® 45 mg is indicated for the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

1. ELIGARD® 45 mg is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD® 45 mg. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.[2]

2. ELIGARD® 45 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® 45 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 ureteral obstruction 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® 45 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. One patient (<1%) failed to achieve castrate levels. Once suppressed, only one patient (< 1%) experienced a testosterone breakthrough with testosterone levels exceeding 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 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. No carcinogenicity studies have been conducted with ELIGARD® 45 mg.

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.

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

Pediatric Use: ELIGARD® 45 mg is contraindicated in pediatric patients and was not studied in children (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The safety of ELIGARD® 45 mg was evaluated in 111 patients with advanced prostate cancer. ELIGARD® 45 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 AGL0205, 111 patients were dosed with ELIGARD® 45 mg every six months for up to 12 months and injection sites were closely monitored. In all, 217 injections of ELIGARD® 45 mg were administered. Transient burning/stinging was reported at the injection site following 35 (16%) injections, with 32 of 35 (91.4%) of these events reported as mild and three of 35 (8.6%) reported as moderate. Mild pain was reported following nine (4.1%) study injections and moderate pain was reported following one (<1%) study injection (total of 2.7% of patients). Mild bruising was reported following five (2.3%) study injections and moderate bruising was reported following two (< 1%) study injections.

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 of up to 12 months of treatment with ELIGARD® 45 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 = 111) Treated with ELIGARD® 45 mg for up to 12 Months in Study AGL0205

Body System	Adverse Event	Number	Percent
Vascular	Hot flashes*	64	57.7%
General Disorders	Fatigue	13	11.7%
	Weakness	4	3.6%
Reproductive	Testicular atrophy*	8	7.2%
	Gynecomastia*	4	3.6%
Skin	Night sweats*	3	2.7%
Musculoskeletal	Myalgia	5	4.5%
	Pain in limb	3	2.7%

In addition, the following possibly or probably related systemic adverse events were reported by 1% of the patients using ELIGARD® 45 mg in the clinical study.

General: Lethargy
Reproductive: Penile shrinkage*
Renal/Urinary: Nocturia, nocturia aggravated
Psychiatric: Loss of libido*

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* Expected pharmacological consequences of testosterone suppression. In the patient population studied, a total of 89 hot flash adverse events were reported in 64 patients. Of these, 62 events (70%) were mild; 27 (30%) were moderate.

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® 45 mg is one injection every six months. The injection delivers 45 mg of leuprolide acetate, incorporated in a polymer formulation. It is administered subcutaneously and provides continuous release of leuprolide for six months.

Once mixed, ELIGARD® 45 mg should be discarded if not administered within 30 minutes.

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).

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® 45 MG PRIOR TO ADMINISTRATION:

ELIGARD® 45 mg is packaged in either thermoformed trays or pouches. Each carton contains:

- One sterile Syringe A pre-filled with the ATRIGEL® polymer system
- One Syringe B pre-filled with leuprolide acetate powder
- One long white plunger rod for use with Syringe B
- One sterile 19-gauge, 5/8-inch needle
- Desiccant pack(s)

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

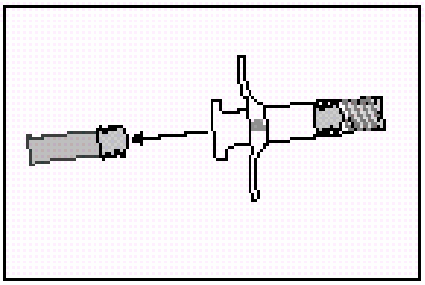


Figure 3

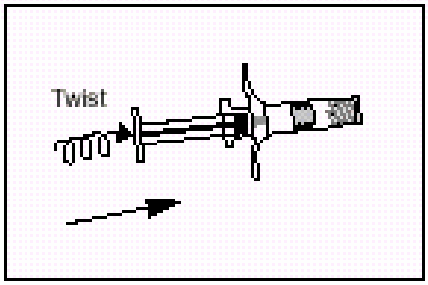


Figure 4

2. **Pull out the blue-tipped short plunger rod and attached stopper from Syringe B and discard (Figure 3).** Gently insert the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B by twisting it in place (Figure 4).

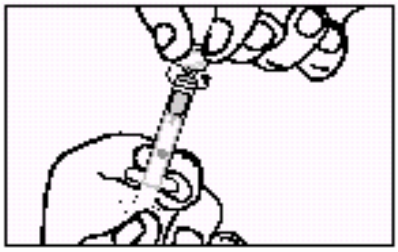


Figure 5

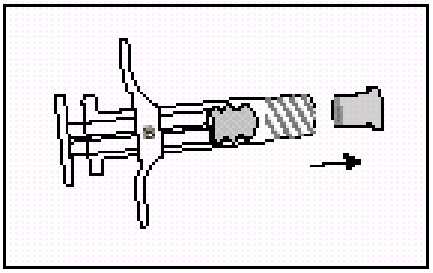


Figure 6

3. Unscrew the clear cap from Syringe A (Figure 5). Remove the gray rubber cap from Syringe B (Figure 6).

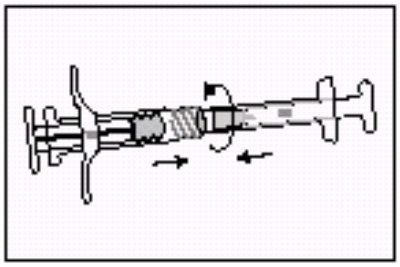


Figure 7

4. Join the two syringes together by pushing in and twisting until secure (Figure 7).

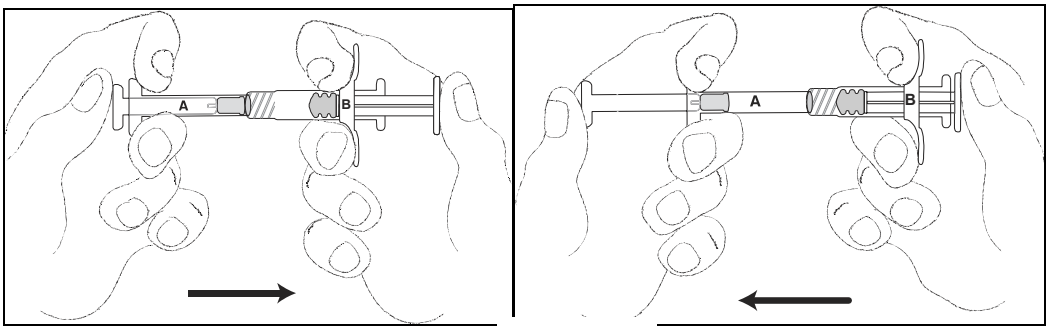


Figure 8

5. Inject the liquid contents of Syringe A into Syringe B containing the leuprolide acetate. 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 8). When thoroughly mixed, the suspension will appear colorless to pale yellow in color. **Please note: Product must be mixed as described; shaking will not provide adequate mixing of the product.**

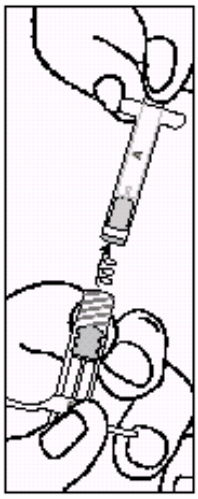


Figure 9

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 9). **Please note: Small air bubbles will remain in the formulation – this is acceptable.**

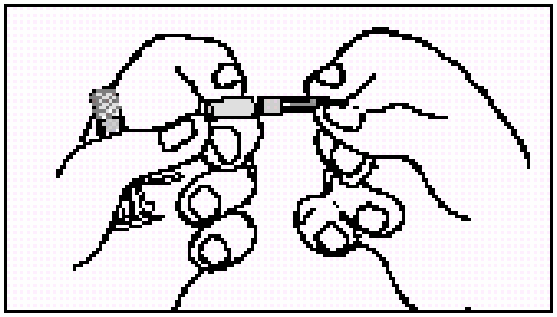


Figure 10

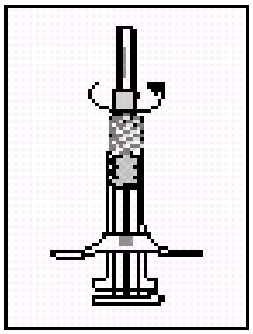


Figure 11

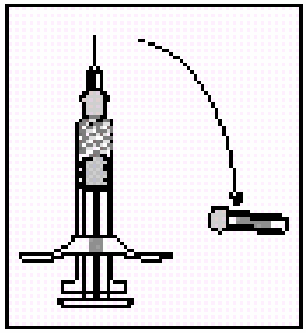


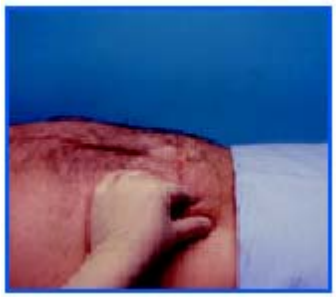
Figure 12

7. Hold Syringe B upright. Remove the yellow cap on the bottom of the sterile needle cartridge by twisting it (Figure 10). Attach the needle cartridge to the end of Syringe B (Figure 11) 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 12).

Administration Procedure

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

1. Choose an injection site on the abdomen, upper buttocks, or anywhere with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Since you can vary the injection site with a subcutaneous injection, 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 nondominant hand, grab and bunch the area of skin around the injection site.

4. Using your dominant hand, insert the needle quickly. The approximate angle you use will depend on the amount and fullness of the subcutaneous tissue and the length of the needle.

5. After the needle is inserted, release the skin with your nondominant hand.

6. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.
7. Withdraw the needle quickly at the same angle used for insertion.
8. Discard all components safely in an appropriate biohazard container.

HOW SUPPLIED

ELIGARD® 45 mg is available in a single use kit. The kit consists of a two-syringe mixing system, a 19-gauge 5/8-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® 45 mg is administered as a single dose.

(NDC xxxxx-xxx-xx)

Rx only

Store at 2 - 8 °C (35.6 – 46.4 °F)

<Sanofi-Synthelabo logo>

Manufactured for Sanofi-Synthelabo Inc.
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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.