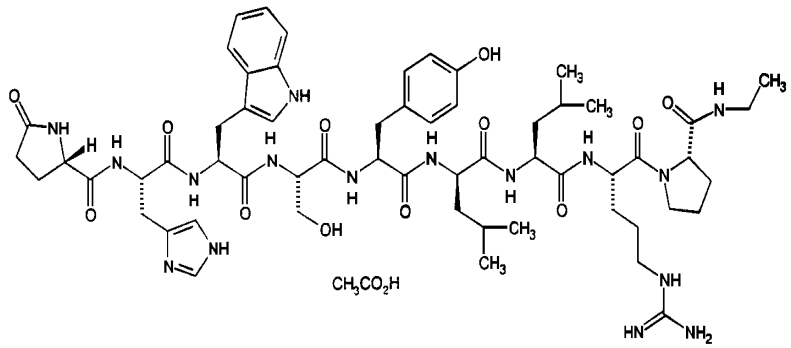
ELIGARD™ 30 mg
(leuprolide acetate for injectable suspension)

DESCRIPTION

ELIGARD™ 30 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30 mg of leuprolide acetate at a controlled rate over a four-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 (salt) with the following structural formula:



ELIGARD™ 30 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™ 30 mg is administered once every four 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 30 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD™ 30 mg delivers 30 mg of leuprolide acetate (equivalent to approximately 28 mg leuprolide free base) dissolved in 258.5 mg *N*-methyl-2-pyrrolidone and 211.5 mg poly(DL-lactide-co-glycolide). The approximate weight of the administered formulation is 500 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 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.

PHARMACODYNAMICS

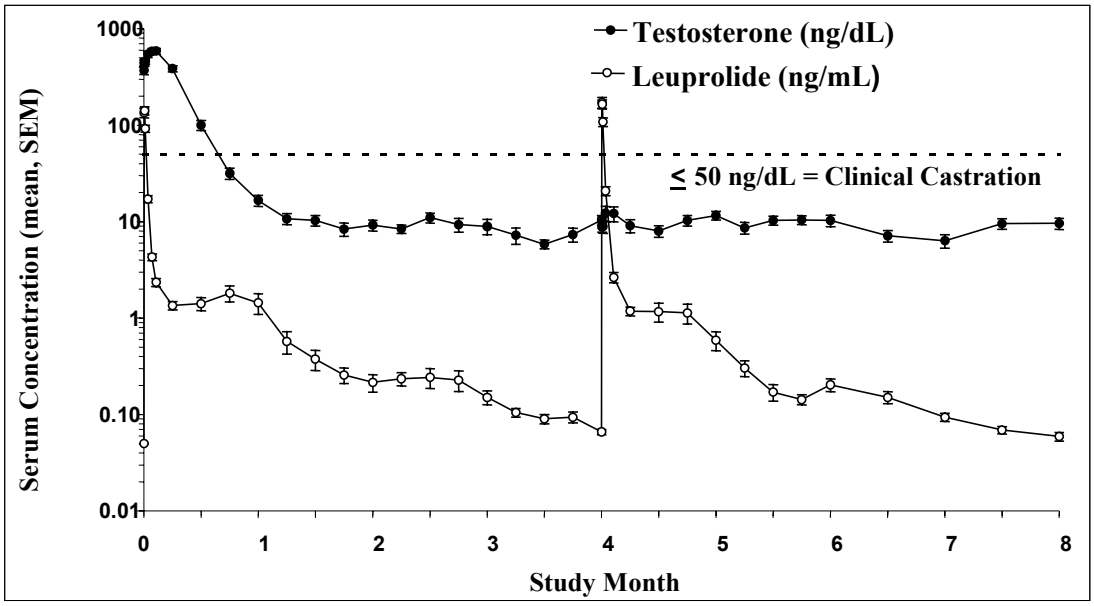
Following the first dose of ELIGARD™ 30 mg, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold ($\leq$ 50 ng/dL) within three weeks (Figure 1). One patient withdrew from the study at Day 14. Of the 89 patients remaining in the study, 85 (96%) had serum 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, 3 patients (3%) 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 four months (ELIGARD™ 30 mg) in 24 patients with advanced carcinoma of the prostate is shown in Figure 1. Mean serum leuprolide concentrations following the initial injection rose rapidly to 150 ng/mL (Cmax) 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). There was no evidence of significant accumulation during repeated dosing. Nondetectable leuprolide plasma concentrations have been occasionally observed during ELIGARD™ 30 mg administration, but testosterone levels were maintained at castrate levels.

Figure 1. Pharmacokinetic/Pharmacodynamic Response (N = 24) to ELIGARD™ 30 mg - Patients dosed initially and at Month 4



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

No drug metabolism study was conducted with ELIGARD™ 30 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™ 30 mg.

Special Populations:
Geriatrics: The majority (71%) of the 90 patients studied in the clinical trial were age 70 and older.

Pediatrics: The safety and effectiveness of ELIGARD™ 30 mg in pediatric patients have not been established (see **CONTRAINDICATIONS**).

Race: In patients studied (18 White, 4 Black, 2 Hispanic), mean serum leuprolide concentrations were similar.

Renal and Hepatic Insufficiency: The pharmacokinetics of ELIGARD™ 30 mg in hepatically and renally impaired patients have not been determined.

Drug-Drug Interactions: No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD™ 30 mg.

CLINICAL STUDIES

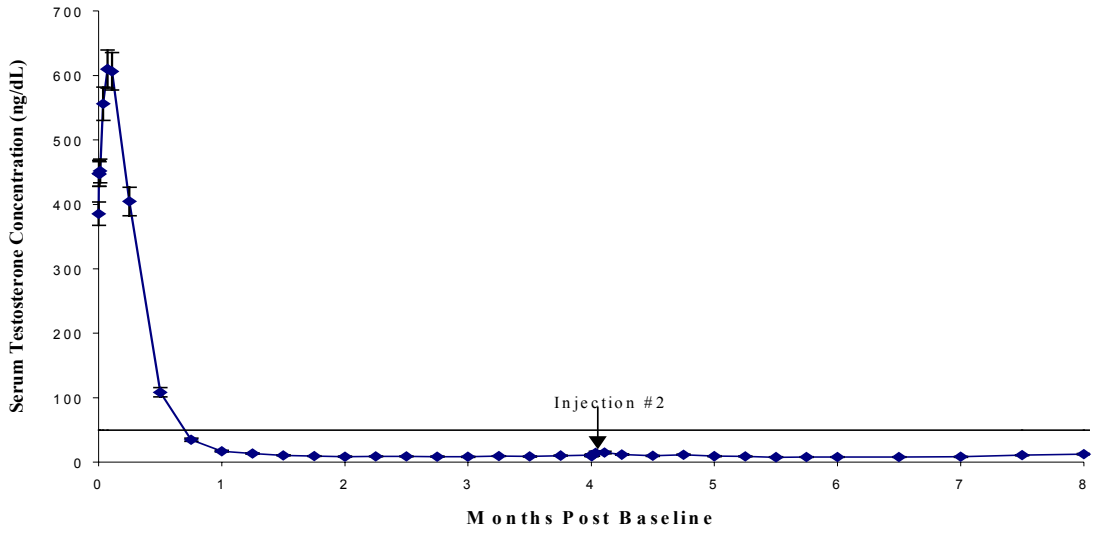
In one open-label, multicenter study (AGL0001), 90 patients with prostate cancer were treated with at least a single injection of study drug. Of these, 85 patients received a total of two injections of ELIGARD™ 30 mg given once every four months. Two patients had Jewett stage A disease, 38 had stage B disease, 16 had stage C disease and 34 patients had stage D disease. This study evaluated the achievement and maintenance of castrate serum testosterone suppression over eight months of therapy. A total of 82 patients completed the study.

The mean testosterone concentration increased from 385.5 ng/dL at Baseline to 610.0 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 17.2 ng/dL on Day 28. At the conclusion of the study (Month 8), mean testosterone concentration was 12.4 ng/dL (Figure 2).

Of the original 90 patients, one patient withdrew on Day 14. Serum testosterone was suppressed to below the castrate threshold ($\leq$ 50 ng/dL) by Day 28 in 85 of 89 (96%) patients remaining in the study. All 89 (100%) of patients remaining in the study attained the castrate threshold by Day 42. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, three patients (3%) demonstrated breakthrough (concentration above 50 ng/dL) during the study. 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 timepoints. 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 above 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. Of 82 evaluable patients in the study at Month 8, 81 had testosterone concentrations of $\leq$ 50 ng/dL.

All seven 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™ 30 mg Mean Serum Testosterone Concentrations (n = 90)



Serum PSA decreased in all patients whose Baseline values were elevated above the normal limit. Mean values were reduced 86% from Baseline to Month 8. At Month 8, PSA levels had decreased to within normal limits in 93% 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) and 10% as "restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature" (Status=1). At Month 8, the percentage of fully active men decreased slightly to 87%, the percentage of men classified as restricted increased slightly to 12%, and one patient (1%) was classified as unable to carry out work activities (Status=2). At Baseline, patients experienced little bone pain, with a mean score of 1.20 (range 1-7) on a scale of 1 (no pain) to 10 (worst pain possible). At Month 8, the mean bone pain score was essentially unchanged at 1.19 (range 1-8). Urinary pain, scored on the same scale, was similarly low, with a mean of 1.01 at Baseline (range 1-2) and all patients had a score of 1 by Month 8. Urinary signs and symptoms were similarly low at Baseline and decreased modestly at Month 8. In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 66 (73%) at Screening to 54 (60%) at Month 8.

INDICATIONS AND USAGE

ELIGARD™ 30 mg is indicated for the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

1. ELIGARD™ 30 mg is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD™ 30 mg. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.[ii]

2. ELIGARD™ 30 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™ 30 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™ 30 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 third week. Castrate levels were generally reached within two to four weeks, with most (86/89) patients remaining suppressed throughout the study.

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 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™ 30 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™ 30 mg is contraindicated in pediatric patients and was not studied in children (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The safety of ELIGARD™ 30 mg was evaluated in 90 patients with advanced prostate cancer. ELIGARD™ 30 mg, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first week 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 AGL0001, 90 patients were dosed with ELIGARD™ 30 mg every four months for up to eight months and injection sites were closely monitored. In all, 175 injections of ELIGARD™ 30 mg were administered. Transient burning/stinging was reported at the injection site following 35 (20%) injections, with all (100%) of these events reported as mild. Pain was reported following 2.3% of study injections (3.3% of patients) and was generally reported as mild in intensity. A single event reported as moderate pain resolved within two minutes and all 3 mild pain events resolved within several days. Erythema was reported following 1.1% of injections (2.2% of patients). These events were all reported as mild and generally resolved within a few days post-injection.

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 eight months of treatment with ELIGARD™ 30 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 = 90) Treated with ELIGARD™ 30 mg for up to Eight Months in Study AGL0001

Body System	Adverse Event	Number	Percent
Vascular	Hot flashes*	66	73.3%
General Disorders	Fatigue	12	13.3%
Reproductive	Testicular atrophy*	4	4.4%
	Gynecomastia*	2	2.2%
	Testicular pain	2	2.2%
Skin	Clamminess*	4	4.4%
	Night sweats*	3	3.3%
	Alopecia	2	2.2%
Renal/Urinary	Nocturia	2	2.2%
	Urinary frequency	2	2.2%
Nervous system	Dizziness	4	4.4%
Psychiatric	Decreased libido*	3	3.3%
Musculoskeletal	Myalgia	2	2.2%
Gastrointestinal	Nausea	2	2.2%

In addition, the following possibly or probably related systemic adverse events were reported by 1.1% of patients using ELIGARD™ 30 mg in the clinical study.

General: Lethargy
Reproductive: Breast enlargement*, erectile dysfunction*, reduced penis size
Renal/Urinary: Urinary urgency, incontinence
Psychiatric: Insomnia, depression
Musculoskeletal: Muscle atrophy, limb pain

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* Expected pharmacological consequences of testosterone suppression. In the patient population studied, 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.

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.[iii] 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™ 30 mg is one injection every four months. The injection delivers 30 mg of leuprolide acetate, incorporated in a polymer formulation. It is administered subcutaneously and provides continuous release of leuprolide for four months.

Once mixed, ELIGARD™ 30 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™ 30 MG PRIOR TO ADMINISTRATION:

ELIGARD™ 30 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).

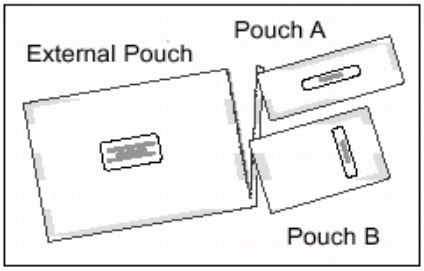


Figure 3

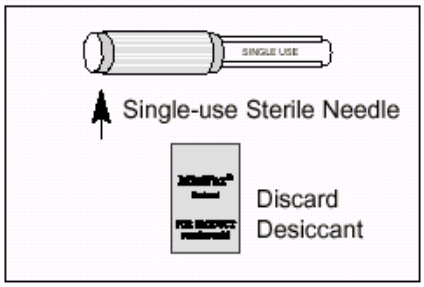


Figure 4

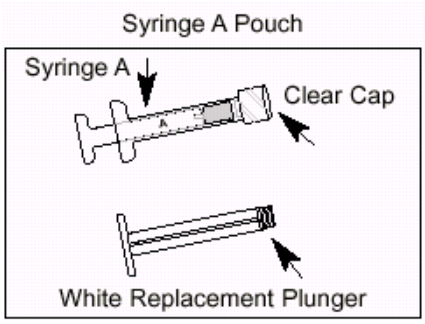


Figure 5

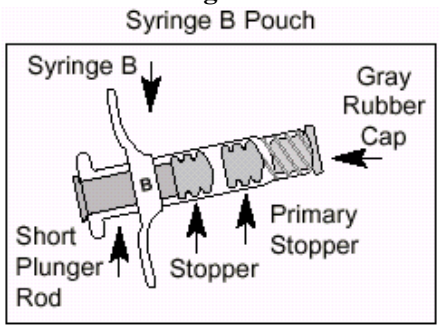


Figure 6

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

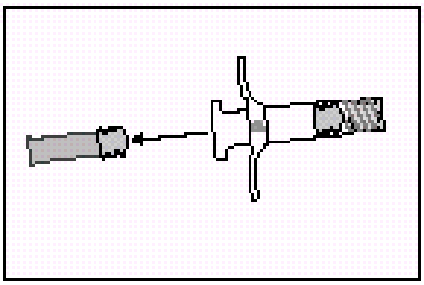


Figure 7

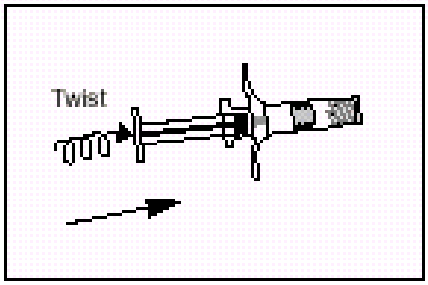


Figure 8

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).

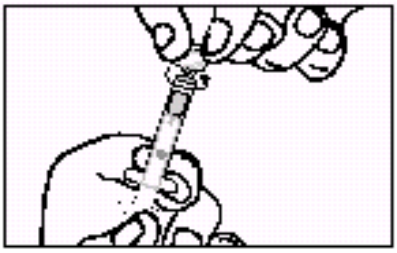


Figure 9

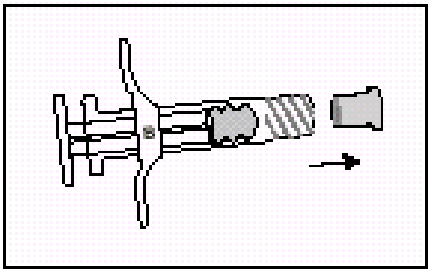


Figure 10

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

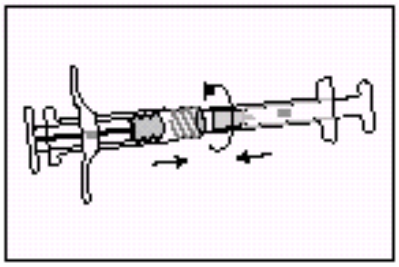


Figure 11

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

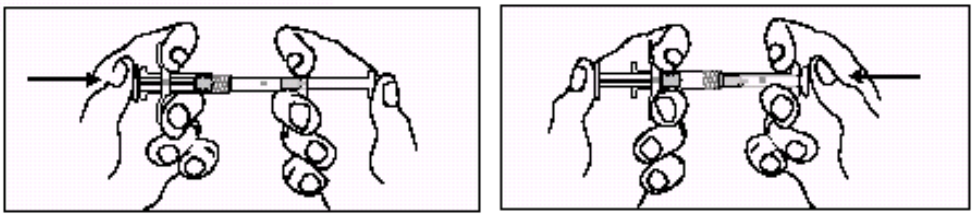


Figure 12

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.**

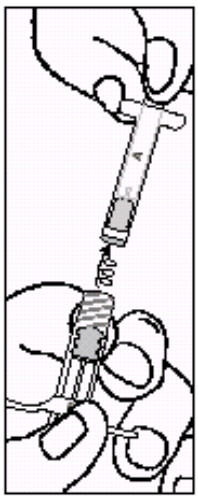
6. 
nges vertically with Syringe B on the bottom. The syringes should
ely coupled. Draw the entire mixed product into Syringe B (short, wide
epressing the Syringe A plunger and slightly withdrawing the Syringe B
couple Syringe A while continuing to push down on the Syringe A
ıre 13). **Please note: Small air bubbles will remain in the
– this is acceptable.**

Figure 13

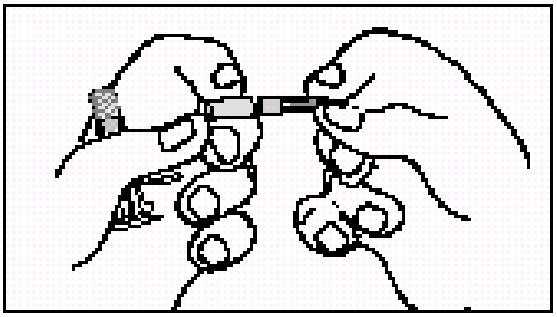


Figure 14

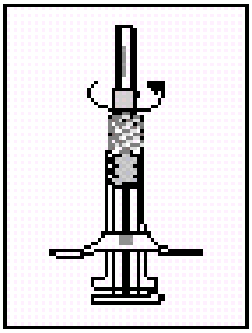


Figure 15

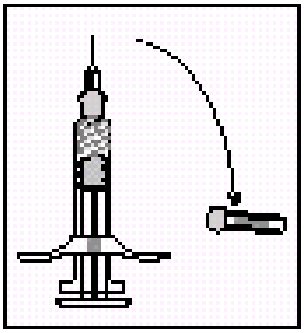


Figure 16

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™ 30 mg is available in a single use kit. The kit consists of a two-syringe mixing system, a 20-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™ 30 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.
New York, NY 10016 by Atrix Laboratories, Inc.,
Fort Collins, CO 80525

04XXXX, Rev 0 x/03

Printed in USA Revised MM/YYYY

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[i] Sennello LT et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. J Pharm Sci 1986; 75(2): 158-160.
[ii] MacLeod TL et. al. Anaphylactic reaction to synthetic luteinizing hormone releasing hormone. Fertil Steril 1987 Sept; 48(3): 500-502.
[iii] 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.