

## PRODUCT MONOGRAPH

**PrELIGARD®**

(Leuprolide acetate for injection)

7.5 mg [1-Month]  
22.5 mg [3-Month]  
30 mg [4-Month] &

(Leuprolide acetate for injectable suspension)

45 mg [6-Month]

### **THERAPEUTIC CLASSIFICATION**

Luteinizing Hormone-Releasing Hormone Analog

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**Table of Contents**

**PART I: HEALTH PROFESSIONAL INFORMATION..... 3**

- SUMMARY PRODUCT INFORMATION ..... 3
- INDICATIONS AND CLINICAL USE..... 3
- CONTRAINDICATIONS ..... 4
- WARNINGS AND PRECAUTIONS..... 4
- ADVERSE REACTIONS..... 9
- DRUG INTERACTIONS ..... 13
- DOSAGE AND ADMINISTRATION ..... 14
- OVERDOSAGE ..... 31
- ACTION AND CLINICAL PHARMACOLOGY ..... 32
- STORAGE AND STABILITY..... 36
- SPECIAL HANDLING INSTRUCTIONS ..... 36
- DOSAGE FORMS, COMPOSITION AND PACKAGING ..... 37

**PART II: SCIENTIFIC INFORMATION ..... 39**

- PHARMACEUTICAL INFORMATION..... 39
- CLINICAL TRIALS ..... 40
- DETAILED PHARMACOLOGY ..... 44
- MICROBIOLOGY ..... 45
- TOXICOLOGY ..... 45
- REFERENCES ..... 49

**PART III: CONSUMER INFORMATION..... 51**

## Pr **ELIGARD**<sup>®</sup>

(Leuprolide acetate for injection / Leuprolide acetate for injectable suspension)

### **PART I: HEALTH PROFESSIONAL INFORMATION**

#### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Subcutaneous injection	<p>Lyophilised powder for injection ( solution after constituted with ATRIGEL<sup>®1</sup> polymer system)</p> <ul style="list-style-type: none"><li>7.5 mg [1-Month] (10.2 mg/BD syringe or 10.6 mg/Schott syringe to deliver 7.5 mg leuprolide acetate)</li><li>22.5 mg [3-Month] (28.2 mg/BD syringe or 29.2 mg/Schott syringe to deliver 22.5 mg leuprolide acetate)</li><li>30 mg [4-Month] (35.8 mg/BD syringe or 37.2 mg/Schott syringe to deliver 30 mg leuprolide acetate)</li></ul> <p>Lyophilised powder for injection ( suspension after constituted with ATRIGEL<sup>®</sup> polymer system)</p> <ul style="list-style-type: none"><li>45 mg [6-Month] (58.2 mg/BD syringe or 59.2 mg/Schott syringe to deliver 45 mg leuprolide acetate)</li></ul>	N-methyl-2-pyrrolidone Poly (DL-lactide-co-glycolide)

#### **INDICATIONS AND CLINICAL USE**

ELIGARD (leuprolide acetate) is indicated for the palliative treatment of advanced prostate cancer (stage D2).

ELIGARD should be administered by a health care professional.

##### **Geriatrics (> 70 years of age):**

The majority (> 70%) of the patients studied in the clinical trials for ELIGARD were 70 years and older (See CLINICAL TRIALS).

##### **Pediatrics (< 12 years of age):**

The safety and effectiveness of ELIGARD in pediatric patients have not been established (See WARNINGS AND PRECAUTIONS).

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<sup>1</sup> ATRIGEL<sup>®</sup> is a registered trade mark of TOLMAR Therapeutics, Inc.

## CONTRAINDICATIONS

ELIGARD is contraindicated in patients with hypersensitivity to Luteinizing Hormone-Releasing Hormone (LH-RH), LH-RH analogs or any of the components of ELIGARD. Anaphylactic reactions including anaphylactic shock to synthetic LH-RH or LH-RH analogs have been reported in post-marketing surveillance. For a complete listing, see the Dosage Forms, Composition and Packaging section.

ELIGARD is contraindicated in women who are, or may become, pregnant while receiving the drug. There are possibilities that fetal harm and spontaneous abortions may occur. The use of ELIGARD in nursing mothers is not recommended.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

ELIGARD (leuprolide acetate) should be prescribed by a qualified physician experienced in the use of hormonal therapy in prostate cancer.

The following are clinically significant adverse events:

- Clinical testosterone flare reaction in men with prostate cancer (see **General** below)
- Pituitary apoplexy (see **Endocrine and Metabolism** below)
- Osteoporosis (see **Endocrine and Metabolism** below).

### General

ELIGARD, like other LH-RH analogs, causes a transient increase in serum concentration of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH analogs. If spinal cord compression or renal impairment due to ureteral obstruction develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin leuprolide therapy under close supervision.

Mixing and administration procedures should be followed, as lack of clinical efficacy may occur due to incorrect reconstitution or administration of the product (see Monitoring and Laboratory tests below and DOSAGE AND ADMINISTRATION, Mixing and Administration Procedure).

## **Carcinogenesis and Mutagenesis**

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 were 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 testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumours 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 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.

## **Cardiovascular**

There may be a relationship between androgen deprivation therapy and cardiovascular risk in men with prostate cancer on the basis of the demonstrated adverse impact of androgen deprivation on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity (see REFERENCES section). Reports of events related to cardiovascular ischemia including myocardial infarction, stroke and cardiovascular-related deaths have been received in patients treated with LH-RH agonists.

Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential cardiovascular risk. Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered (see “Monitoring and Laboratory Test” below).

### Effect on QT/QTc interval

Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications.

In a randomized, active-controlled trial to compare leuprolide acetate 7.5 mg with a LH-RH antagonist in patients with prostate cancer, periodic electrocardiograms were collected. The analysis of the pooled data in the leuprolide cohort (n= 46 patients) showed a mean QTcF increase of 17 msec from baseline; the percentage of subjects who experienced a QTcF change of  $\geq 30$  msec and  $\geq 60$  msec from baseline was 41% (n = 19 patients) and 4% (n = 2 patients), respectively.

## **Dependence/Tolerance**

No drug dependence has been reported with the use of leuprolide.

## **Endocrine and Metabolism**

### Pituitary apoplexy

During post-marketing surveillance, serious cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of LH-RH agonists including ELIGARD. The majority of the cases occurred within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden onset of severe headache, vomiting, progressive symptoms of visual disturbance, ophthalmoplegia, altered mental status, hypopituitarism, and sometimes cardiovascular collapse. Immediate medical attention is required. Pre-existing gonadotropin-secreting pituitary adenoma was diagnosed in a majority of patients. If the presence of macroadenomas is evidenced by imaging and biochemical assessments, this should be surgically removed prior to start of LH-RH agonist including ELIGARD treatment.

### Changes in bone density:

Decreased bone mineral density can be anticipated with long term use of an LHRH agonist. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal bone fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, ELIGARD may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with ELIGARD is instituted.

### Hypogonadism

Long-term administration of leuprolide will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

### Reduction in glucose tolerance

A reduction in glucose tolerance and an increased risk in developing diabetes have been reported in men treated with androgen deprivation therapy. Patients treated with LH-RH agonists should undergo periodic monitoring of blood glucose. Diabetic patients may require more frequent monitoring when receiving LH-RH agonists.

## **Hematologic**

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

## **Renal and Hepatic**

All clinical studies and kinetic evaluations have been conducted in patients with adequate hepatic and renal function.

## **Respiratory:**

There have been postmarketing reports of interstitial pneumonitis associated with leuprolide acetate use. Treatment should be discontinued immediately if the patient develops any signs or symptoms suggestive of interstitial lung disease.

## **Neurologic**

Convulsions have been reported in patients treated with ELIGARD in the post-marketing setting.

## **Special Populations**

### ***Pregnant Women:***

ELIGARD is contraindicated in women who are, or may become pregnant while receiving the drug and in women who are nursing, as safety and effectiveness have not been established in this group of patients.

### ***Nursing Women:***

ELIGARD is not indicated for use in nursing women as safety and effectiveness have not been established in this group of patients.

### ***Pediatrics (< 12 years of age):***

ELIGARD is not indicated for use in children as safety and effectiveness have not been established in this group of patients.

### ***Geriatrics (> 70 years of age):***

The majority (> 70%) of the patients studied in the clinical trials for ELIGARD were 70 years and older.

### ***Race:***

In clinical pharmacokinetic studies, mean serum leuprolide concentration profiles were similar among subjects after administration of ELIGARD 7.5 mg (26 White, 2 Black), ELIGARD 22.5 mg (19 White, 4 Black, 2 Hispanic), ELIGARD 30 mg (18 White, 4 Black, 2 Hispanic), and ELIGARD 45 mg (17 White, 7 Black, 3 Hispanic).

## **Monitoring and Laboratory Tests**

Renal function tests, blood urea nitrogen (BUN) and creatinine may rarely be elevated during the first few days of therapy in prostate cancer patients before returning to normal. In clinical trials with ELIGARD however, no significant difference was observed from baseline to 7 days following injection in terms of the number of patients who demonstrated an elevation from normal to above normal levels of creatinine and BUN.

Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving ELIGARD should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Blood glucose levels and/or glycosylated hemoglobin (HbA1c) should be checked periodically in patients treated with LH-RH agonists and more frequently in diabetic patients (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Response to ELIGARD may be monitored by periodically measuring serum concentrations of testosterone and prostate specific antigen. 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.

Testosterone levels should also be evaluated in case of suspected or known handling errors, as lack of efficacy may result from incorrect preparation or administration.

The effects of leuprolide on bone lesions may be monitored by bone scans, while its effects on prostatic lesions may be monitored by ultrasonography, and/or CT scan in addition to digital rectal examination. Intravenous pyelogram, ultrasonography, or CT scan may also be utilized to diagnose or assess the status of obstructive uropathy.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

ELIGARD, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first 2 weeks of treatment (first week of treatment for 4-Month and 6-Month). Therefore, potential exacerbations of signs and symptoms of the disease during the first few 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 clinical trials of non-orchietomized prostate cancer patients treated with ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg, none of the 1338 injections and subsequent transient increases in testosterone were associated with an exacerbation of disease symptoms.

Some adverse effects reported with ELIGARD are due primarily to its pharmacological action of sex hormone suppression. The safety of ELIGARD 7.5 mg (1-Month) and ELIGARD 22.5 mg (3-Month) was evaluated in orchietomized and non-orchietomized patients with advanced prostate cancer in three clinical trials. The safety of ELIGARD 30 mg (4-Month) and ELIGARD 45 mg (6-Month) was evaluated in 50 and 63 patients with advanced prostate cancer, respectively.

Local adverse events reported after injection of ELIGARD 7.5 mg (1-Month), ELIGARD 22.5 mg (3-Month), ELIGARD 30 mg (4-Month) and ELIGARD 45 mg (6-Month) were typical of those frequently associated with similar subcutaneously injected products and included transient burning and stinging (27.5 % of injections) and pain at the site of injection (3.9 % of injections), which were typically mild in intensity, brief in duration (one minute or less) and non-recurrent over time.

The majority of study injections were not associated with reports of injection site adverse events.

Other local adverse events that were rarely reported (< 2.6%) following the administration of ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg included erythema (1.7%), bruising (2.0%), pruritus (0.8%), induration and ulceration (0.3%). These events were mostly reported as mild and generally resolved within a few days post injection.

## Clinical Trial Adverse Drug Reactions

*ELIGARD 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) and 45 mg (6-Month)*

The following possibly or probably related systemic adverse events were reported by  $\geq 2\%$  of the patients using ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg in clinical studies:

**Table 1.** Incidence (%) of possibly or probably related Systemic Adverse Events reported by  $\geq 2\%$  of patients treated with **ELIGARD 7.5 mg** [1 injection every month for up to 6 months], **ELIGARD 22.5 mg** [1 injection every 3 months for up to 6 months], **ELIGARD 30 mg** [1 injection every 4 months for up to 8 months] and **ELIGARD 45 mg** [1 injection every 6 months for up to 12 months].

		<b>7.5 mg (n=128)</b>	<b>22.5 mg (n= 117)</b>	<b>30 mg (n= 90)</b>	<b>45 mg (n= 111)</b>
<b>Body System</b>	<b>Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Body as a whole	Malaise & Fatigue	21 (16.4)	-	-	-
	Dizziness	4 (3.1)	-	4 (4.4)	-
Cardiovascular	Vasodilation/ Hot Flashes/ Flushing*	70 (54.7)	66 (56.4)	66 (73.3)	64 (57.7)
General disorders	Fatigue	See Body as a whole	7 (6.0)	12 (13.3)	13 (11.7)
	Weakness	-	-	-	4 (3.6)
Genitourinary	Atrophy of the Testes*	6 (4.7)	-	4 (4.4)	8 (7.2)
	Testicular pain	-	-	2 (2.2)	-
	Gynecomastia*	-	-	2 (2.2)	4 (3.6)
Digestive	Gastroenteritis/ Colitis	3 (2.3)	-	-	-
Gastrointestinal	Nausea	-	4 (3.4)	2 (2.2)	-
Musculoskeletal	Arthralgia	-	4 (3.4)	-	-
	Myalgia	-	-	2 (2.2)	5 (4.5)
	Pain in Limb	-	-	-	3 (2.7)
Renal and Urinary	Urinary frequency	-	3 (2.6)	2 (2.2)	-
	Nocturia	-	-	2 (2.2)	-
Skin	Pruritus (not otherwise specified)	-	3 (2.6)	-	-
	Alopecia	-	-	2 (2.2)	-
	Clamminess*	-	-	4 (4.4)	-
	Night Sweats*	-	-	3 (3.3)	3 (2.7)
Psychiatric	Decreased Libido*	-	-	3 (3.3)	-

\* Expected pharmacological consequences of testosterone suppression.

In the ELIGARD 7.5 mg clinical trial, hot flashes were reported as mild in 80% of patients, moderate in 18.6 % of patients and severe in 1.4 % of patients. A total of 84 hot flashes/flushing events were reported in the ELIGARD 22.5 mg clinical trial; of these, 73 of 84 (87%) were described as mild and 11 of 84 (11%) as moderate. No severe events were reported in the

ELIGARD 22.5 mg study. In the patient population studied for ELIGARD 30 mg, a total of 75 hot flashes were reported in 66 patients. Of these, 57 events (76%) were described as mild; 16 (21%) as moderate; 2 (3%) as severe. A total of 89 hot flash events were reported in the ELIGARD 45 mg study. Of these, 62 events (70%) were described as mild and 27 events (30%) as moderate.

### **Less Common Clinical Trial Adverse Drug Reactions (<2%)**

The following possibly or probably related systemic adverse events were reported by < 2% of the patients using ELIGARD 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) and 45 mg (6-Month) in clinical studies.

#### **ELIGARD 7.5 mg (1-Month)**

General:	Sweating, insomnia, syncope
Gastrointestinal:	Flatulence, constipation
Hematologic:	Decreased red blood cell count, hematocrit and hemoglobin (anemia)
Metabolic:	Weight gain
Musculoskeletal:	Tremor, backache, joint pain
Nervous:	Disturbance of smell and taste, depression, vertigo
Skin:	Alopecia
Urogenital:	Testicular soreness, impotence, decreased libido, gynecomastia, breast soreness

#### **ELIGARD 22.5 mg (3-Month)**

Cardiovascular:	Hypertension, hypotension
General:	Rigors, weakness, lethargy, pain (not otherwise specified), fever
Urinary:	Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine and urinary retention
Reproductive and breast:	Breast tenderness, testicular atrophy and pain, enlarged breasts, impotence
Gastrointestinal:	Stomach upset, constipation, dry mouth

#### **ELIGARD 30 mg (4-Month)**

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

\* Expected pharmacological consequence of testosterone suppression

#### **ELIGARD 45 mg (6- month)**

In addition, the following possibly or probably related systemic adverse events were reported by 1% of the patients (2/111) using ELIGARD 45 mg in the clinical study:

General:	Lethargy
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Reproductive: Penile disorder\*  
Renal/ Urinary: Nocturia, aggravated nocturia  
Psychiatric: Loss of libido\*  
\* Expected pharmacological consequence of testosterone suppression

### **Abnormal Hematologic and Clinical Chemistry Findings**

Abnormalities of certain parameters were observed, but are difficult to assess in this population. For both ELIGARD 7.5 mg and ELIGARD 22.5 mg abnormal values were observed in  $\geq 5\%$  of the study population for the following analyses at any time during the study: increased eosinophils, neutrophils, BUN, total cholesterol, triglycerides, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and creatine kinase (CK). Decreased red blood cell count, hematocrit, and hemoglobin were observed.

In addition, for ELIGARD 7.5 mg, decreased white blood cells, as well as increased sodium, lactate dehydrogenase (LDH) and International Normalized Ratio (INR) were observed for  $\geq 5\%$  of the study population. For ELIGARD 22.5 mg, increased creatinine and aspartate aminotransferase (AST) were observed in  $\geq 5\%$  of the study population.

### **Post-Market Adverse Drug Reactions**

**Endocrine:** pituitary apoplexy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

**Immune:** Anaphylactic/anaphylactoid reactions including anaphylactic shock.

**Nervous system:** convulsion.

**Muscular system:** Muscular atrophy.

**Respiratory system:** Interstitial lung disease.

## **DRUG INTERACTIONS**

### **Overview**

No formal drug interaction studies have been conducted with ELIGARD. No data is available on the interaction with alcohol.

### **Drug-Drug Interactions**

Interactions with drugs have not been established.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of ELIGARD with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g. quinidine, disopyramide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine), antidepressants (e.g. amitriptyline, nortriptyline), opioids (e.g. methadone), macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. quinine), azole antifungals, 5-hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists (e.g. ondansetron), and beta-2 adrenoceptor agonists (e.g. salbutamol).

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Therapy with leuprolide 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.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

ELIGARD should be administered by a health care professional.

ELIGARD 7.5, 22.5, 30 and 45 mg administered subcutaneously is designed to provide continuous sustained release of leuprolide for 1, 3, 4 and 6 months, respectively.

### **Recommended Dose and Dosage Adjustment**

#### *ELIGARD 7.5 mg (1-Month)*

The recommended dose of ELIGARD (1-Month) is 7.5 mg administered monthly as a single subcutaneous injection after mixing with a special polymer formulation (see ADMINISTRATION). The total deliverable injection weight per dose is 250 mg including 7.5 mg leuprolide acetate. The total volume administered per dose is approximately 0.25 mL.

#### *ELIGARD 22.5 mg (3-Month)*

The recommended dose of ELIGARD (3-Month) is 22.5 mg administered every three months as a single subcutaneous injection after mixing with a special polymer formulation (see ADMINISTRATION). The total deliverable injection weight per dose is 375 mg including 22.5 mg of leuprolide acetate. The total volume administered per dose is approximately 0.37 mL.

#### *ELIGARD 30 mg (4-Month)*

The recommended dose of ELIGARD 30 mg (4-Month) is 30 mg administered every four months as a single subcutaneous injection after mixing with a special polymer formulation (see ADMINISTRATION). The total deliverable injection weight per dose is 500 mg including 30 mg of leuprolide acetate. The total volume administered per dose is approximately 0.50 mL.

#### *ELIGARD 45 mg (6-Month)*

The recommended dose of ELIGARD 45 mg (6-Month) is 45 mg administered every six months as a single subcutaneous injection after mixing with a special polymer formulation (see ADMINISTRATION). The total deliverable injection weight per dose is 375 mg including 45 mg of leuprolide acetate. The total volume administered per dose is approximately 0.375 mL.

### **Missed Dose**

Maintaining testosterone suppression is important in treating the symptoms of hormone-dependent prostate cancer. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of ELIGARD injections is an important part of treatment.

### **Administration**

As with other drugs administered by subcutaneous injection, the injection site should be varied 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).

As with all parenteral drug products, syringes as well as reconstituted drug solutions, should be inspected visually for particulate matter, precipitate, discoloration and leakage prior to administration. Solutions showing particulate matter, precipitate, discoloration or leakage should not be used.

Prior to administration, the syringes are removed from the trays, the syringe tip caps are removed, and the syringes are coupled. The product is prepared by passing the formulation from syringe to syringe until a homogenous solution (homogenous suspension for ELIGARD 45 mg product) is achieved. The syringes are decoupled and the safety needle is affixed to the male syringe.

### **Mixing and Administration Procedure**

**ELIGARD 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) & 45 mg (6-Month)**

#### **IMPORTANT:**

- **Follow the instructions as directed to ensure proper preparation of ELIGARD prior to administration. If the product is not prepared using the proper technique, it should not be administered, as lack of clinical efficacy may occur.**
- Allow the product to reach room temperature by removing from the refrigerator at least 30 min before mixing. However, before reconstitution, ELIGARD can be stored at room temperature (15 – 30°C) in original packaging, for a period of 8 weeks prior to administration.
- **ONLY** use ATRIGEL<sup>®</sup> polymer system to reconstitute the product, in order to ensure providing the continuous sustained release of the product.
- Once mixed, the product must be administered within 30 minutes, as the viscosity of the solution increases with time.
- The product must be administered via subcutaneous injection only.

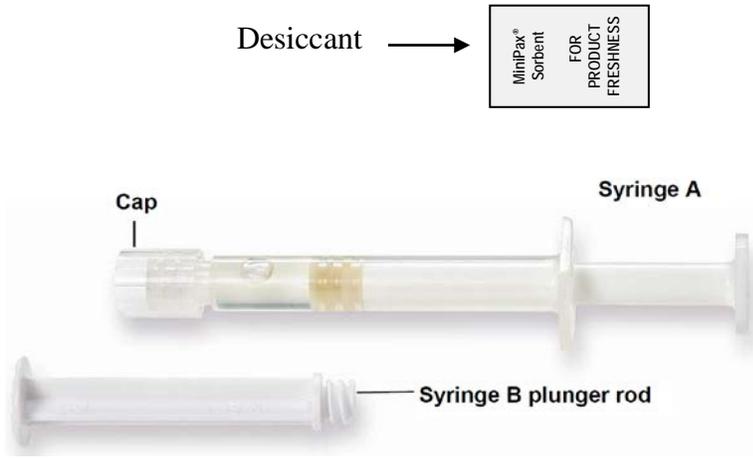
As with other similar agents, the use of gloves is recommended during mixing and administration.

ELIGARD is packaged in tray packaging.

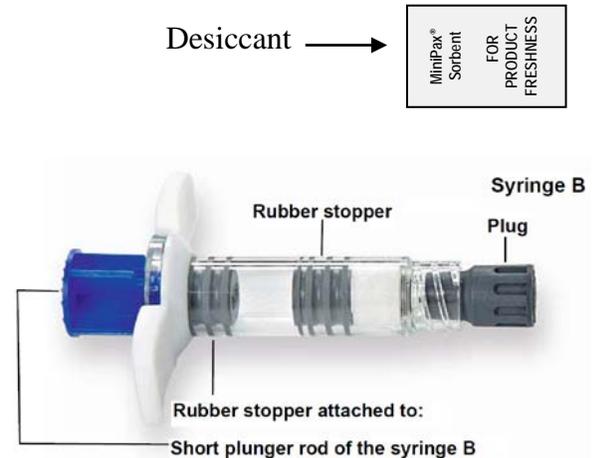
The tray packaging contains two thermoformed trays. One tray contains the sterile Syringe A pre-filled with the ATRIGEL<sup>®</sup> polymer system, a long white replacement plunger rod and a desiccant pouch (Figure 1). The other tray contains the sterile Syringe B pre-filled with leuprolide acetate powder, a sterile safety needle cartridge and a desiccant pouch (Figure 2). The two trays are placed into a paperboard carton.

## Tray packaging

**Figure 1**



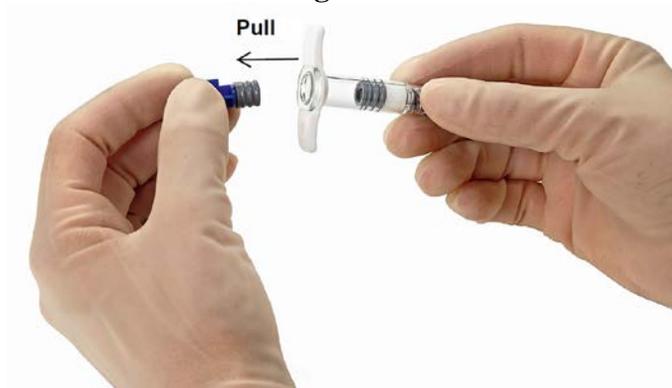
**Figure 2**



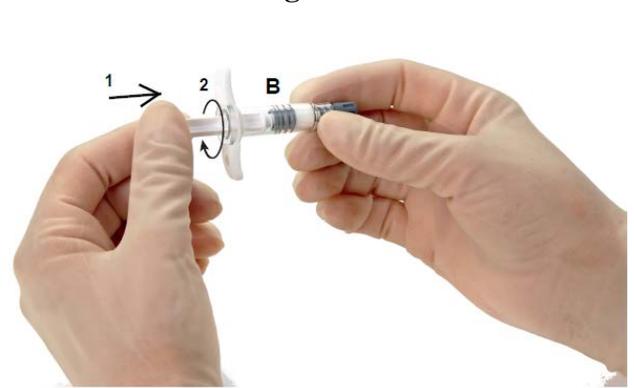
### A. Administration procedure – syringe used with the Terumo®<sup>2</sup> safety needle

1. On a clean field, open all trays and remove the contents. Discard the desiccant packs.
2. Pull out the blue-tipped short plunger rod (do not unscrew) 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 3**



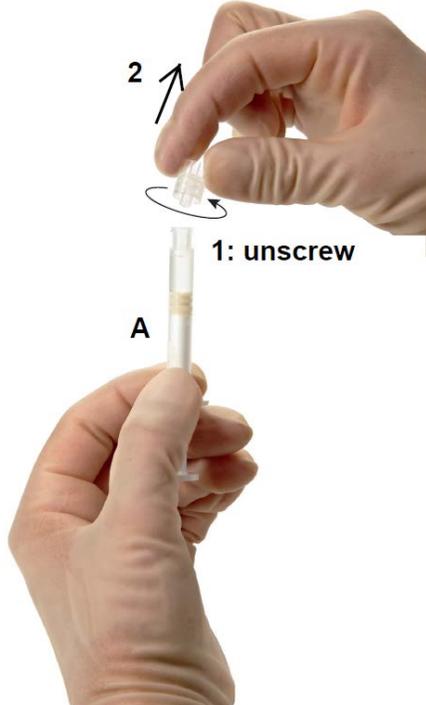
**Figure 4**



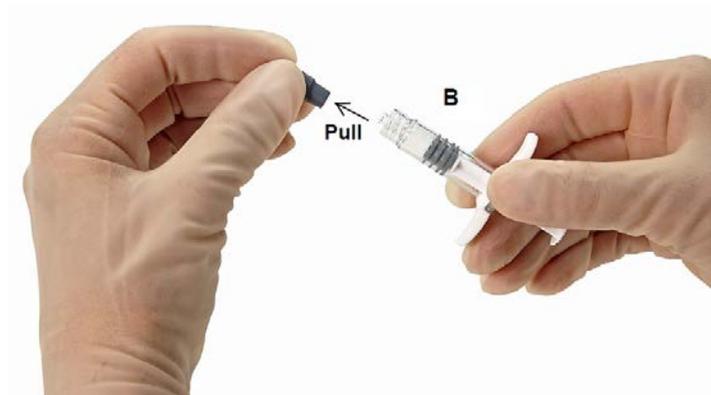
<sup>2</sup> Terumo® is a registered trademark of Terumo Corporation

3. Hold Syringe A in a vertical position to ensure no liquid leaks out. Unscrew the clear cap from Syringe A (Figure 5). Remove the gray rubber cap from Syringe B (Figure 6).

**Figure 5**

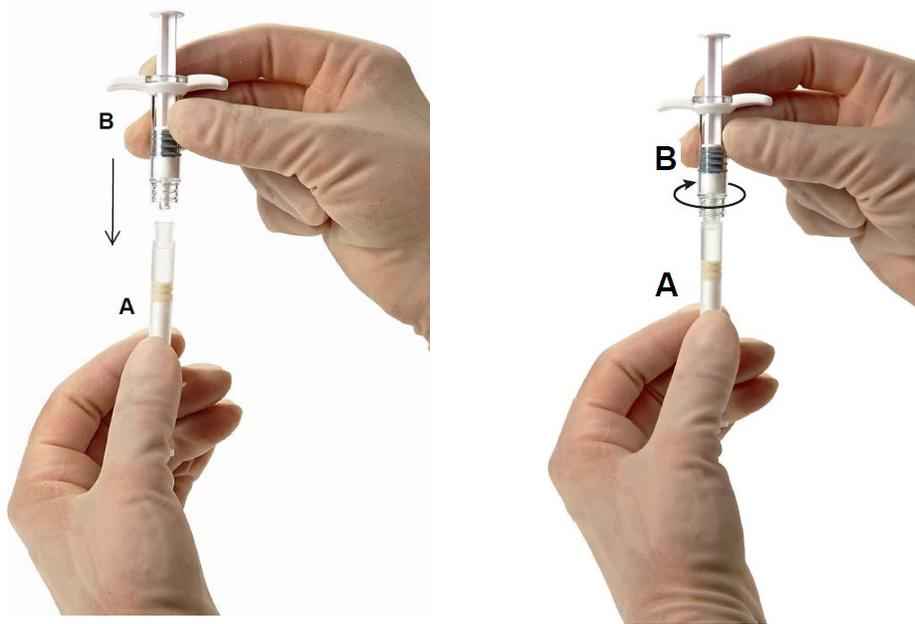


**Figure 6**



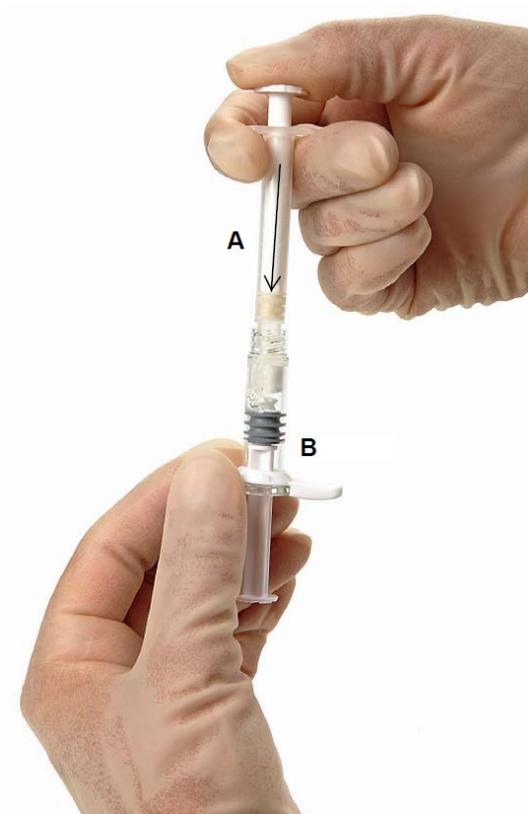
4. Join the two syringes together by pushing in and twisting until secure (Figure 7). Do not over tighten. The needle cartridge will not secure properly, if any of the liquid has leaked out.

**Figure 7**

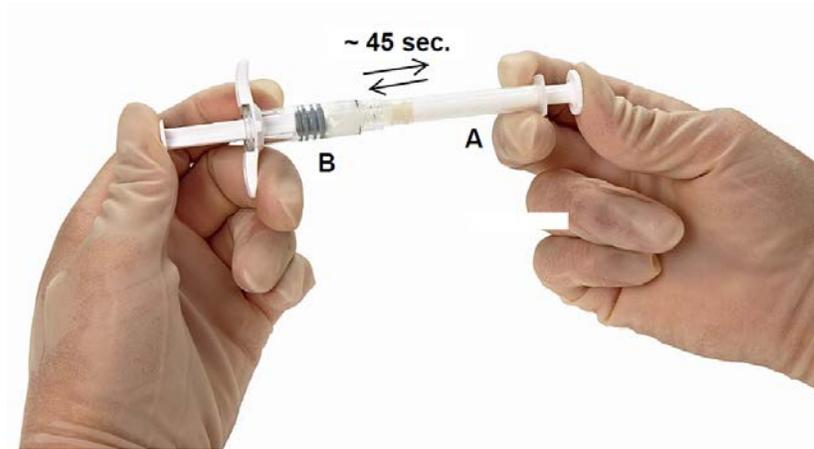


- Inject the liquid contents of Syringe A into Syringe B containing the leuprolide acetate. Thoroughly mix the product by pushing the contents of both syringes back and forth between syringes (approximately 45 seconds), in a horizontal position, to obtain a uniform solution (suspension for ELIGARD 45 mg product) (Figure 8 and Figure 9). Do not bend the syringe system. When thoroughly mixed, the solution (suspension for ELIGARD 45 mg product) will appear a colourless to tan color. **Please note:** Product must be mixed as described; shaking WILL NOT provide adequate mixing of the product.

**Figure 8**

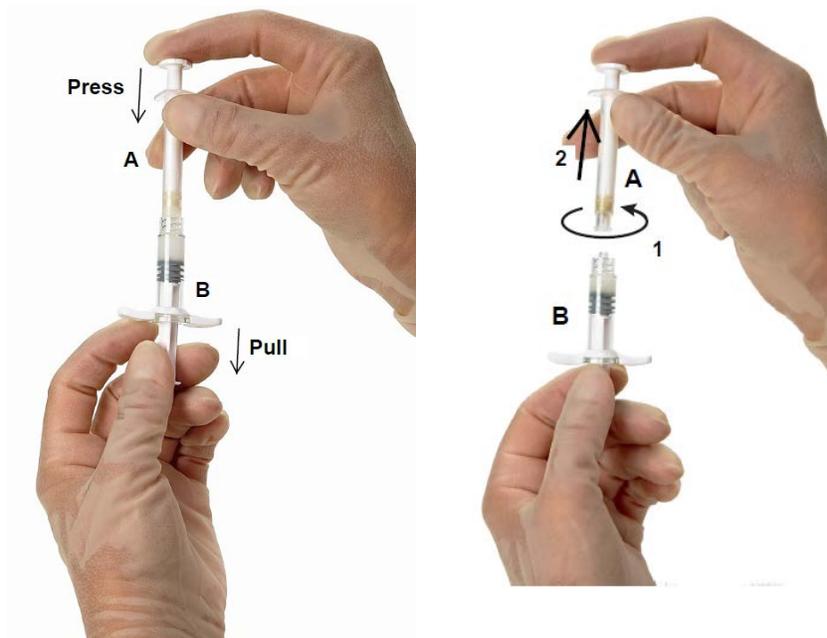


**Figure 9**



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 10). Please note: Small air bubbles will remain in the formulation - this is acceptable.

**Figure 10**

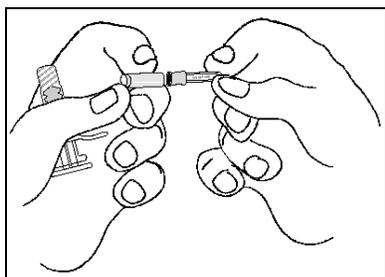


7. Hold Syringe B upright and hold back the white plunger to prevent loss of the product. Open the pack of the safety needle by peeling back the paper tab halfway but do not remove completely from the packaging at this time. To prevent contamination, be careful not to touch the needle's luer connector. When attaching the needle, hold the needle's blister pack and aseptically attach to the syringe as instructed (Figure 11). Attach the safety needle cartridge to the end of Syringe B (Figure 12) with a push and a clockwise twist motion. **Do not overtighten** as this may cause cracking of the needle hub resulting in leakage of the product during injection. Should the needle hub crack, appear to be damaged, or have any leakage, the product should not be used. The damaged needle should not be substituted/replaced and the product should not be injected. The entire product should be disposed of securely. In the event of damage to the needle hub, a new replacement product should be used. Keep hands behind needle at all times during use and disposal.

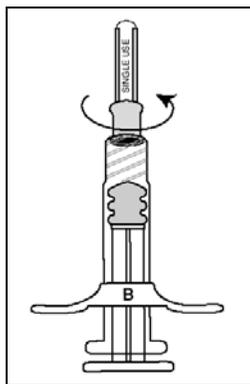
Cautions:

- If the needle is bent or damaged, no attempt should be made to straighten needle or use the product.
- If the safety sheath is activated, do not attempt to deactivate it by forcing the needle out of the safety sheath.

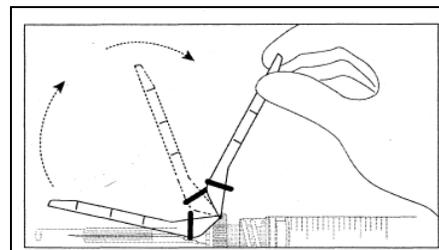
**Figure 11**



**Figure 12**



**Figure 13**



8. Move the safety sheath away from the needle and toward the syringe barrel to an approximate 90° angle. The sheath will remain as set (Figure 13).
9. 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.
10. Cleanse the injection-site area with an alcohol swab.
11. Pull off the clear needle cartridge cover prior to administration.

12. Using the thumb and forefinger of your nondominant hand, grab and bunch the area of skin around the injection site.



13. 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.



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

15. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.

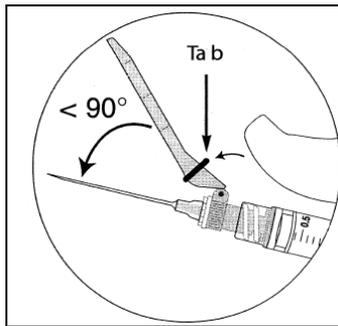


16. Withdraw the needle quickly at the same angle used for insertion. Do not replace the original needle cover after the use.

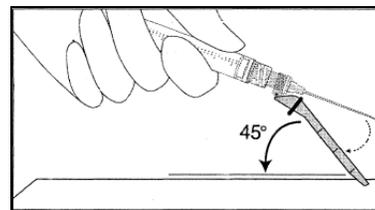
17. Activate the safety sheath by following the instructions described below:

- using a one-handed technique, push the tab forward with your finger or thumb so that the sheath is less than  $90^\circ$  from the needle (Figure 14). Keep your finger or thumb behind the tab at all times;
- position sheath about  $40^\circ - 45^\circ$  to a hard, flat surface (Figure 15);
- with a firm, quick motion, press down against a flat surface until an audible click is heard (Figure 16). (Note: audible click may not be heard; visual confirmation is required);
- visually confirm that the sheath is fully engaged (Figure 17).

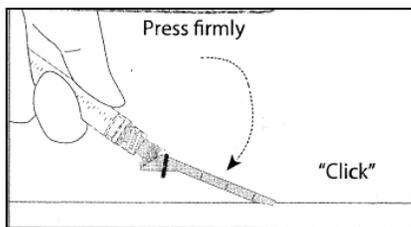
**Figure 14**



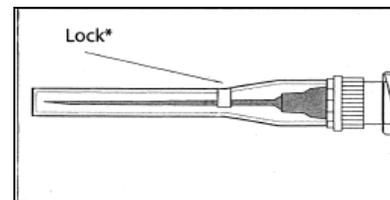
**Figure 15**



**Figure 16**



**Figure 17**



\* Note: the location of the lock will vary depending upon needle size.

Activation of the safety sheath may cause minimum splatter of fluid that may remain on the needle after the injection. For greatest safety, activate the safety sheath using one-handed technique away from self and others.

18. Gently massage the injection area with a cotton ball or gauze pad.

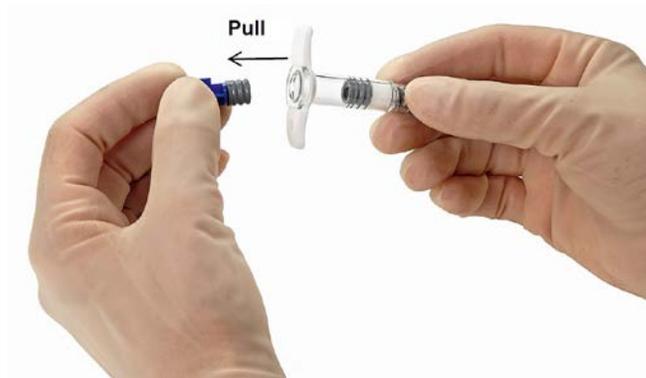
19. Discard all components safely in an appropriate biohazard container.

20. Remove your gloves and wash your hands. Document both the procedure and the patient's response to the injection.

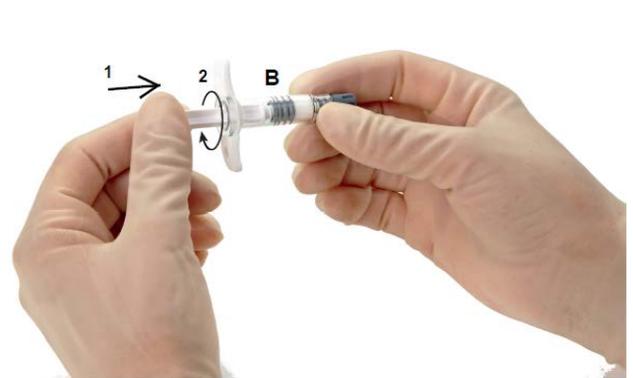
**B. Administration procedure – syringe used with the Magellan<sup>® 3</sup> safety needle**

1. On a clean field, open all trays and remove the contents. Discard the desiccant packs.
2. Pull out the blue-tipped short plunger rod (do not unscrew) and attached stopper from Syringe B and discard (Figure 18). Gently insert the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B by twisting it in place (Figure 19).

**Figure 18**



**Figure 19**

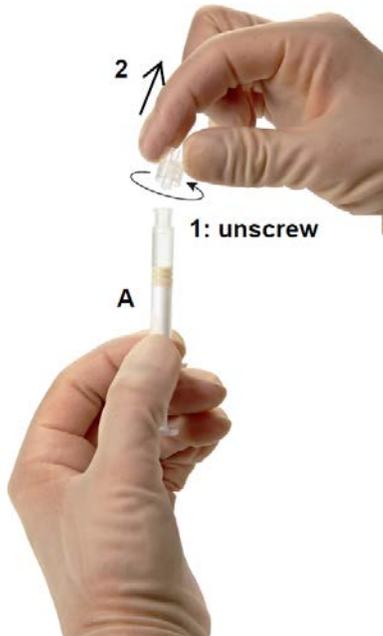


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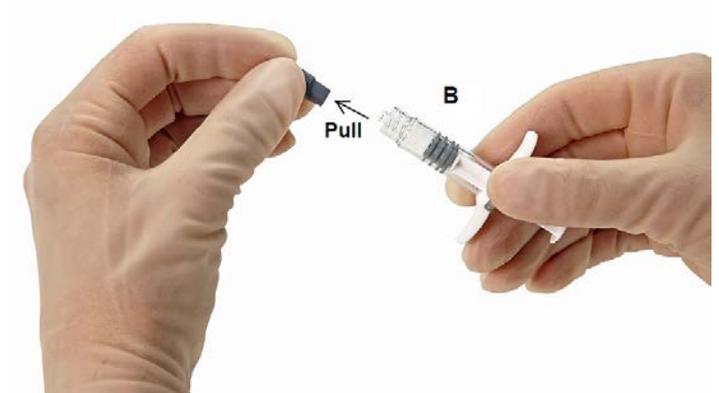
<sup>3</sup> Magellan<sup>®</sup> is a registered trademark of Covidien LLC

3. Hold Syringe A in a vertical position to ensure no liquid leaks out. Unscrew the clear cap from Syringe A (Figure 20). Remove the gray rubber cap from Syringe B (Figure 21).

**Figure 20**

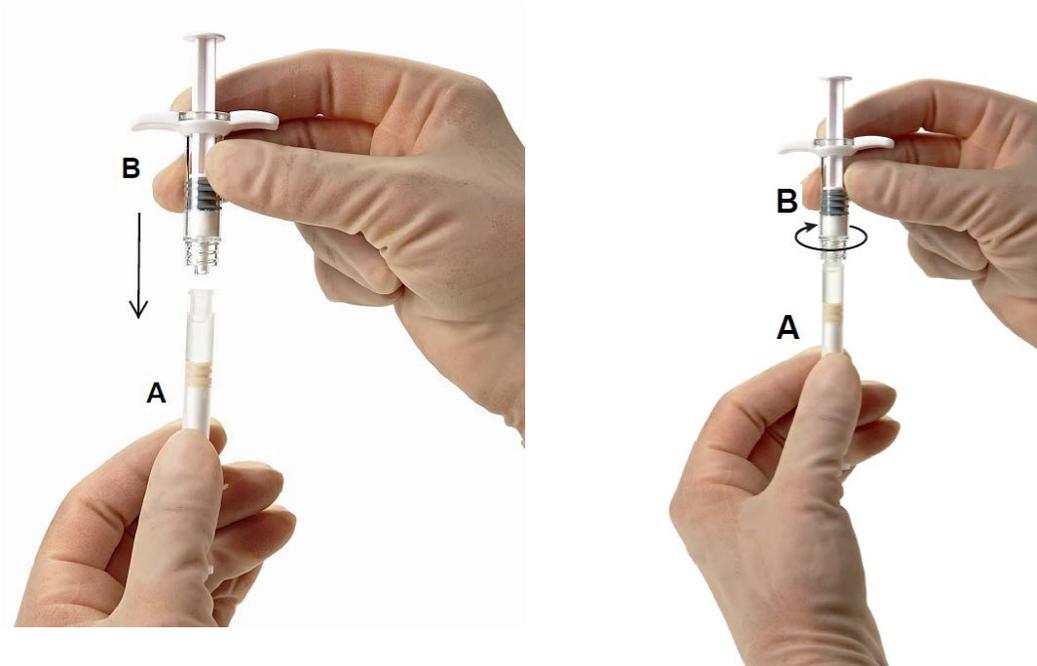


**Figure 21**



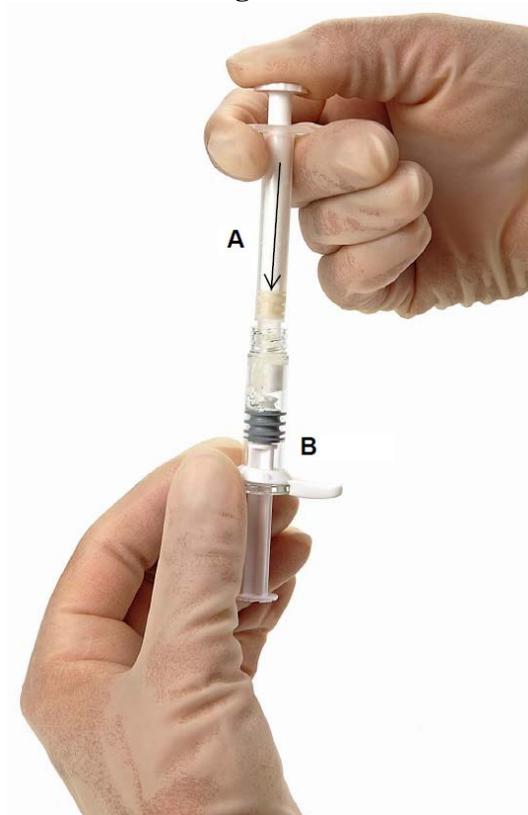
4. Join the two syringes together by pushing in and twisting until secure (Figure 22 ). Do not over tighten. The needle cartridge will not secure properly, if any of the liquid has leaked out.

**Figure 22**

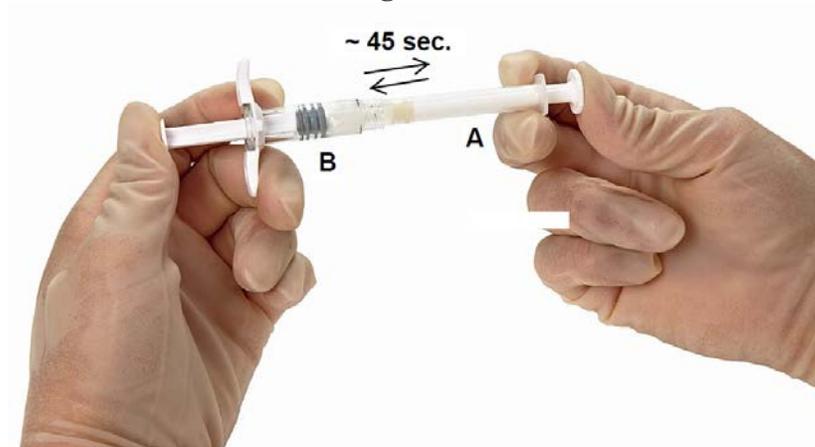


- Inject the liquid contents of Syringe A into Syringe B containing the leuprolide acetate. Thoroughly mix the product by pushing the contents of both syringes back and forth between syringes (approximately 45 seconds), in a horizontal position, to obtain a uniform solution (suspension for ELIGARD 45 mg product) (Figure 23 and Figure 24 ). Do not bend the syringe system. When thoroughly mixed, the solution (suspension for ELIGARD 45 mg product) will appear a colourless to tan color. **Please note:** Product must be mixed as described; shaking WILL NOT provide adequate mixing of the product.

**Figure 23**

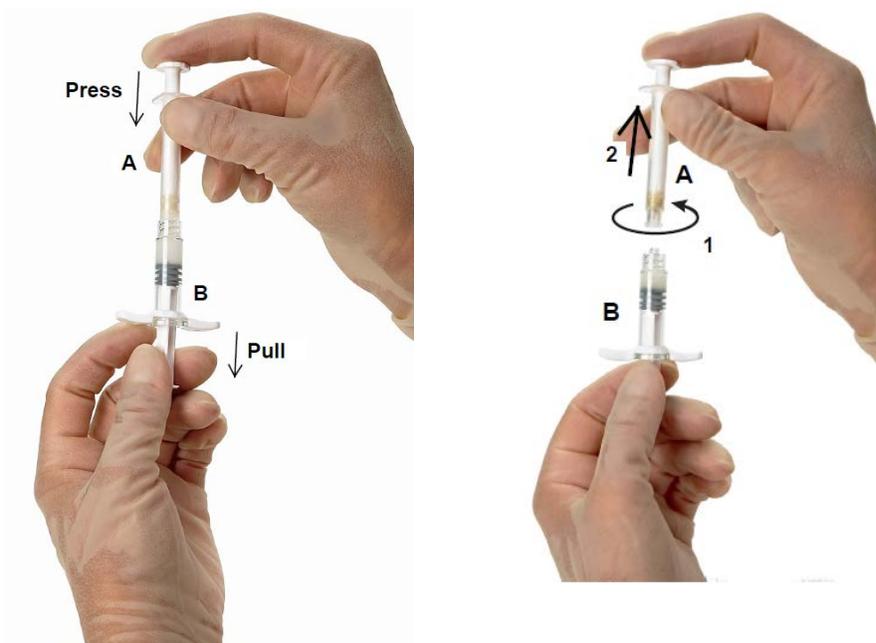


**Figure 24**



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 25). Please note: Small air bubbles will remain in the formulation - this is acceptable.

**Figure 25**



7. Keep the Syringe B upright and hold back the white plunger to prevent loss of the product. Open the pack of the safety needle by peeling back the paper tab halfway but do not remove completely from the packaging at this time. To prevent contamination, be careful not to touch the needle's luer connector. When attaching the needle, hold the needle's blister pack and aseptically attach to the syringe as instructed. Secure the safety needle cartridge to the end of Syringe B by holding the needle and twisting the syringe clockwise to fully seat the needle. **Do not overtighten** as this may cause cracking of the needle hub resulting in leakage of the product during injection. Should the needle hub crack, appear to be damaged, or have any leakage, the product should not be used. The damaged needle should not be substituted/replaced and the product should not be injected. The entire product should be disposed of securely. In the event of damage to the needle hub, a new replacement product should be used. Remove the protective needle sheath.



8. 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.
9. Cleanse the injection-site area with an alcohol swab.
10. Using the thumb and forefinger of your nondominant hand, grab and bunch the area of skin around the injection site.



11. 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.



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

13. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.



14. Withdraw the needle quickly at the same angle used for insertion. Do not replace the original needle cover after the use.

15. Lock the safety shield using any of the following activation methods: thumb, finger or flat surface.



16. Verify locked position through audible and tactile “click”. Locked position will completely cover the needle tip.



17. Gently massage the injection area with a cotton ball or gauze pad.
18. Discard all components safely in an appropriate biohazard container.
19. Remove your gloves and wash your hands. Document both the procedure and the patient's response to the injection.

## **OVERDOSAGE**

There is no clinical experience with the effects of an acute overdose. Because the acute animal toxicity of the drug is low, adverse effects are not expected. No difference in adverse reactions was observed in patients who subcutaneously received either 1 or 10 mg/day leuprolide for up to three years or 20 mg/day for up to two years.

For management of suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring luteinizing hormone-releasing hormone (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. Leuprolide acetate is chemically unrelated to steroids.

Unlike steroid hormones, leuprolide exerts specific action on the pituitary gonadotrophs and the human reproductive tract.

This specificity reduces the likelihood of secondary adverse effects such as gynecomastia, thromboembolism, edema, liver and gallbladder involvement.

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 gonadal steroids. However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. As a result, testosterone is reduced in males to levels associated with castration ( $\leq 50$  ng/dL in serum), and estrogen in females is reduced to postmenopausal levels. These decreases are observed within two to four weeks after the start of treatment and are maintained as long as treatment continues. Castrate levels of testosterone in prostate cancer patients have been demonstrated for periods of up to seven years. The effect is reversible upon discontinuation of drug therapy.

ELIGARD is an injectable polymer-based, extended-release formulation of leuprolide acetate. Subcutaneous (SC) injections of 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) and 45 mg (6-Month) of ELIGARD provide sustained levels of leuprolide acetate over the respective dosing intervals, resulting in continuous suppression of gonadal testosterone synthesis.

In the majority of prostate cancer patients administered monthly SC injections of ELIGARD, 7.5 mg (1-Month) and repeated injections of ELIGARD 22.5 mg (3-Month), ELIGARD 30 mg (4-Month), or ELIGARD 45 mg (6-Month) testosterone levels increased above baseline during the first week, declining thereafter at or below baseline levels by the end of the second and third week, respectively. Castrate levels of testosterone were generally reached within two to four weeks of administration and were maintained for the duration of the treatment.

### **Pharmacodynamics**

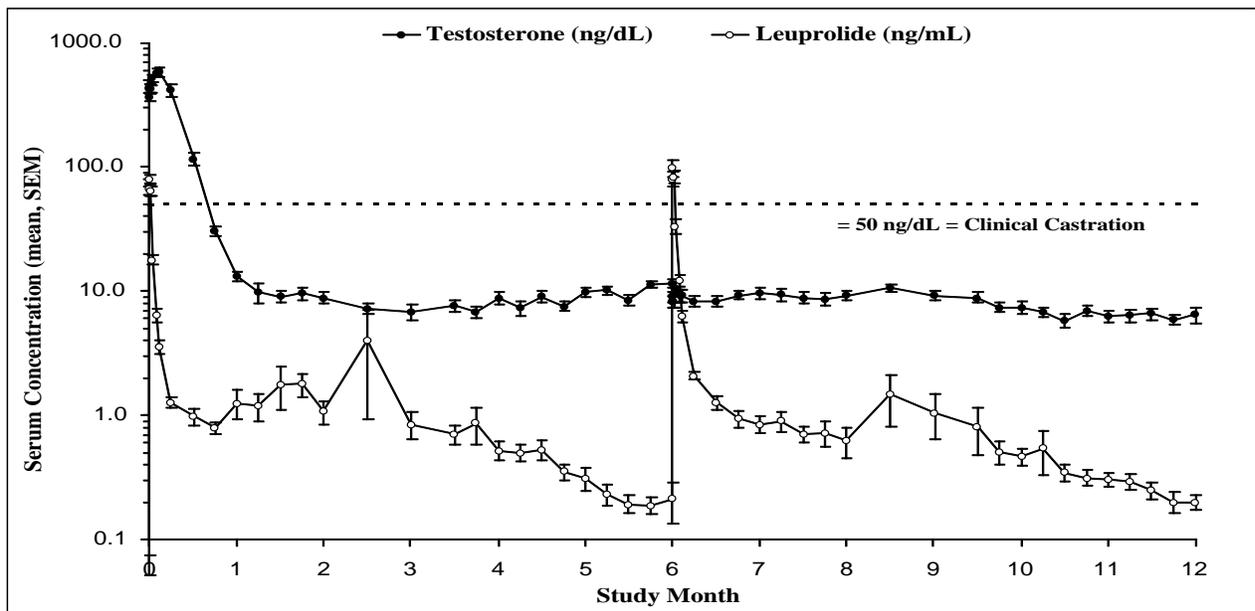
After each injection of ELIGARD 7.5 mg, mean serum leuprolide levels peaked during the first day, then fell rapidly to sustained levels between 0.2-2 ng/mL. In response to this pattern of leuprolide exposure, serum testosterone levels rose initially, from  $408 \pm 60$  ng/dL at baseline to  $600 \pm 74$  ng/dL on Day 3, then fell to below castrate levels ( $\leq 50$  ng/dL) within three weeks after the first dose ( $38 \pm 9$  ng/dL on Day 21). Mean serum testosterone remained relatively constant (7.1 - 17.9 ng/dL) for the rest of the 84-day study.

For ELIGARD 22.5 mg, in response to leuprolide exposure, serum testosterone levels rose initially, to  $610 \pm 246$  ng/dL on Day 2, then fell to below castrate levels ( $\leq 50$  ng/dL) within three weeks after the first dose ( $28 \pm 18$  ng/dL on Day 21). Mean serum testosterone remained relatively constant (7 - 13 ng/dL) for the rest of the six-month (168-day) study, and did not increase following administration of the second dose at month three (Day 84).

After each injection of ELIGARD 30 mg, mean serum leuprolide levels peaked during the first day, then fell rapidly to sustained levels of 0.1 - 1.0 ng/mL. In response to this pattern of leuprolide exposure, mean serum testosterone levels rose initially, from  $385.5 (\pm 18.04)$  ng/dL at baseline, to  $588 \pm 40$  ng/dL on Day 3, then fell to below castrate levels ( $\leq 50$  ng/dL) within 3 weeks after the first dose ( $31.7 \pm 4.2$  ng/dL on Day 21). Levels of testosterone remained between 6 - 12 ng/dL for the remainder of the 224 day study.

The pharmacodynamic response following repeated administration of ELIGARD 45 mg (6-Month) in 28 patients with advanced prostate cancer is shown in Figure 26 (shown below). After each injection, mean serum leuprolide levels peaked during the first day, then fell rapidly to sustained levels of 0.2 - 2.0 ng/mL. In response to this pattern of leuprolide exposure, mean serum testosterone levels rose initially, from  $585 \pm 49$  ng/dL on Day 3, then fell to below castrate levels ( $\leq 50$  ng/dL) within 3 weeks after the first dose ( $30.4 \pm 3.0$  ng/dL on Day 21). Levels of testosterone remained between 6 - 12 ng/dL for the remainder of the 12-month study.

**Figure 26. Pharmacodynamic response to ELIGARD 45 mg (6-Month) showing serum levels of leuprolide (open circles, N= 27) and testosterone (closed circles, N= 28) after two consecutive SC injections at six-month intervals in advanced prostate cancer patients. Doses administered on Day 0 and Month 6 (Day 168).**



Thus, despite the marked fluctuations in serum leuprolide levels resulting from the burst followed by the sustained release profile of ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg

treatment, no clinically significant fluctuations were observed in serum testosterone levels, which remained continuously suppressed once they had fallen to castrate levels. The initial rise and fall in testosterone levels produced by ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg were of a magnitude and timecourse similar to those observed with other leuprolide formulations, and are related to the mechanism by which continuous exposure to LH-RH analogs suppresses gonadal steroidogenesis via hypophyseal desensitization. No acute-on-chronic or breakthrough responses were seen in testosterone concentrations after the second and third dose of ELIGARD.

There were no acute-on-chronic or breakthrough testosterone responses during the burst phase after the second dose of ELIGARD 22.5 mg (3-Month).

No acute-on-chronic responses were seen in testosterone concentrations after the first and second dose of ELIGARD 30 mg (4-Month) and only one patient had a breakthrough response with a single serum testosterone value of 53 ng/dL after the second dose (Day 113). The patient resuppressed at Day 115 and remained suppressed throughout the remainder of the study.

No acute-on-chronic responses were seen in testosterone concentrations after the first and second dose of ELIGARD 45 mg (6-Month) and none of the patients exhibited a breakthrough response during the study.

### **Pharmacokinetics**

#### **Absorption:**

The pharmacokinetics of ELIGARD in patients with advanced prostate cancer were determined over two dosing intervals for ELIGARD 22.5 mg (3-month), ELIGARD 30 mg (4-month) and ELIGARD 45 mg (6-month) and over three dosing intervals for ELIGARD 7.5 mg (1-month). Repeated treatment of advanced prostate cancer patients with ELIGARD products at their intended dosing interval produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After the subcutaneous administration of each ELIGARD depot formulation, an initial burst phase characterized by high serum leuprolide concentrations was followed by a plateau phase during which serum leuprolide concentrations remained relatively constant over the remainder of each dosing interval. There was no evidence of accumulation after repeated administration, with similar serum profiles observed after the first, and each subsequent dose of ELIGARD. Serum leuprolide concentrations during the plateau phase were occasionally below detection, with no effect on testosterone suppression. The sustained-release pharmacokinetic profile of each ELIGARD formulation was associated with continuous testosterone suppression in close to 100% of patients over the intended 1-month, 3-month, 4-month or 6-month dosing interval. See Table 2 below for clinical pharmacokinetic parameters of ELIGARD.

**Table 2: Clinical Pharmacokinetic Parameters for ELIGARD**

Subcutaneous Administration in Patients with Advanced Prostate Cancer								
	Burst Phase (Day 0-3)			Plateau Phase (Day 3-end of interval)			Total Dosing Interval	
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC (ng hr mL <sup>-1</sup> )	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	AUC (ng hr mL <sup>-1</sup> )	C <sub>last</sub> (ng/mL)	AUC (ng hr mL <sup>-1</sup> )
ELIGARD 45 mg (6-month), N=27								
Dose 1	82.0	4.43	1558	6.7	0.12	4362	0.21	5922
Dose 2	102.4	4.75	2357	3.4	0.12	3216	0.20	5573
ELIGARD 30 mg (4-month), N=24								
Dose 1	150	3.3	2080	2.6	0.07	1471	0.08	3551
Dose 2	192	3.0	2659	1.9	0.06	1083	0.07	3743
ELIGARD 22.5 mg (3-month), N=25								
Dose 1	127	4.6	2227	2.4	0.15	1419	0.34	3646
Dose 2	107	4.5	1955	2.7	0.25	1925	0.30	3880
ELIGARD 7.5 mg (1-month), N=8 (single dose study)								
Dose 1	26.3	4.1	350.6	2.69	0.175	514.9	0.36	865.6
ELIGARD 7.5 mg (1-month), N= 20								
Dose 1	25.3	4.6	435.3	2.68	0.169	438.1	0.42	873.4
Dose 2	ND	ND	ND	2.02	0.360	499.6	0.45	ND
Dose 3	ND	ND	ND	1.78	0.328	475.7	0.45	ND

**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. The major metabolite of leuprolide is a pentapeptide (M-1) metabolite. No metabolism study was conducted with ELIGARD.

**Excretion:**

No excretion study was conducted with ELIGARD.

**Special Populations and Conditions**

**Pediatrics:** The safety and effectiveness of ELIGARD in pediatric patients have not been established (see WARNINGS AND PRECAUTIONS).

**Geriatrics:** The majority (> 70%) of the patients studied in the clinical trials for ELIGARD were 70 years and older.

**Gender:** Only male patients were included in studies with ELIGARD.

**Race:** In the patients studied, mean serum leuprolide concentrations were similar. See Table 3 below for race distribution of all subjects in ELIGARD studies.

**Table 3 : Race Distribution of all Subjects in ELIGARD Studies**

	AGL0205 ELIGARD 45 mg study	AGL0001 ELIGARD 30 mg study	AGL9909 ELIGARD 22.5 mg study	AGL9904 ELIGARD 7.5 mg study
White	84 (75.7%)	71 (78.9%)	93 (79.5%)	92 (76.7%)
Black	19 (17.1%)	10 (11.1%)	13 (11.1%)	15 (12.5%)
Hispanic	6 (5.4%)	8 (8.9%)	7 (6.0%)	13 (10.8%)
Asian	1 (0.9%)	0	3 (2.6%)	0
Other	1 (0.9%)	1 (1.1%)	1 (0.9%)	0

**Hepatic and Renal Insufficiency:**

The pharmacokinetics of the drug in hepatically (renally) -impaired patients have not been determined.

**Genetic Polymorphism:** The effect of genetic polymorphism on the pharmacokinetics of ELIGARD was not studied.

**STORAGE AND STABILITY**

ELIGARD should be kept refrigerated between 2-8°C (36-46°F).

ELIGARD can be stored at room temperature (15 – 30 °C) in original packaging for a period of 8 weeks prior to administration.

Once mixed, ELIGARD should be discarded if not used within 30 minutes.

**SPECIAL HANDLING INSTRUCTIONS**

Allow the product to reach room temperature by removing from the refrigerator at least 30 min before reconstitution.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### ***ELIGARD 7.5 mg (1-Month)***

**[10.2 mg (BD syringe) or 10.6 mg (Schott syringe) leuprolide acetate per syringe]**

ELIGARD 7.5 mg (1-Month) is supplied in two separate prefilled, 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. One syringe contains the ATRIGEL<sup>®</sup> Delivery System, and the other contains leuprolide acetate. The ATRIGEL<sup>®</sup> Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, 34% poly (DL-Lactide-co-glycolide) (PLGH) polymer formulation dissolved in a biocompatible solvent, 66% N-methyl-2-pyrrolidone (NMP). PLGH is a co-polymer with a 50:50 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains 10.2 mg (BD syringe) or 10.6 mg (Schott syringe) lyophilized leuprolide acetate and is designed to deliver 7.5 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD 7.5 mg (1-Month) is available in a single use tray packaging, with a safety needle included.

The tray packaging with syringe using a safety needle contains:

- the two-syringe mixing system
- two silica gel desiccant pouches to control moisture uptake
- a 20-gauge one-inch safety needle.

### ***ELIGARD 22.5 mg (3-Month)***

**[28.2 mg (BD syringe) or 29.2 mg (Schott syringe) leuprolide acetate per syringe]**

ELIGARD 22.5 mg (3-Month) is supplied in two separate prefilled, 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. One syringe contains the ATRIGEL<sup>®</sup> Delivery System, and the other contains leuprolide acetate. The ATRIGEL<sup>®</sup> Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, 45% poly (DL-Lactide-co-glycolide)(PLG) polymer formulation dissolved in a biocompatible solvent, 55% N-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains 28.2 mg (BD syringe) or 29.2 mg (Schott syringe) lyophilized leuprolide acetate and is designed to deliver 22.5mg of leuprolide acetate at the time of SC injection.

ELIGARD 22.5 mg (3-Month) is available in a single use tray packaging, with a safety needle included.

The tray packaging with syringe using a safety needle contains:

- the two-syringe mixing system
- two silica gel desiccant pouches to control moisture uptake
- a 20-gauge one-inch safety needle.

***ELIGARD 30 mg (4-Month)***

**[35.8 mg (BD syringe) or 37.2 mg (Schott syringe) leuprolide acetate per syringe]**

ELIGARD 30 mg (4-Month) is supplied in two separate prefilled, 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. One syringe contains the ATRIGEL<sup>®</sup> Delivery System, and the other contains leuprolide acetate. The ATRIGEL<sup>®</sup> Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, 45% poly (DL-Lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible solvent, 55% N-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains 35.8 mg (BD syringe) or 37.2 mg (Schott syringe) lyophilized leuprolide acetate and is designed to deliver 30 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD 30 mg (4-Month) is available in a single use tray packaging, with a safety needle included.

The tray packaging with syringe using a safety needle contains:

- the two-syringe mixing system
- two silica gel desiccant pouches to control moisture uptake
- a 20-gauge one-inch safety needle.

***ELIGARD 45 mg (6-Month)***

**[58.2 mg (BD syringe) or 59.2 mg (Schott syringe) leuprolide acetate per syringe]**

ELIGARD 45 mg (6-Month) is supplied in two separate prefilled, 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. One syringe contains the ATRIGEL<sup>®</sup> Delivery System, and the other contains leuprolide acetate. The ATRIGEL<sup>®</sup> Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, 50% poly (DL-Lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible solvent, 50% N-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 85:15 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains 58.2 mg (BD syringe) or 59.2 mg (Schott syringe) lyophilized leuprolide acetate and is designed to deliver 45 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD 45 mg (6-Month) is available in a single use tray packaging, with a safety needle included.

The tray packaging with syringe using a safety needle contains:

- the two-syringe mixing system
- two silica gel desiccant pouches to control moisture uptake
- a 18-gauge one-inch safety needle.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

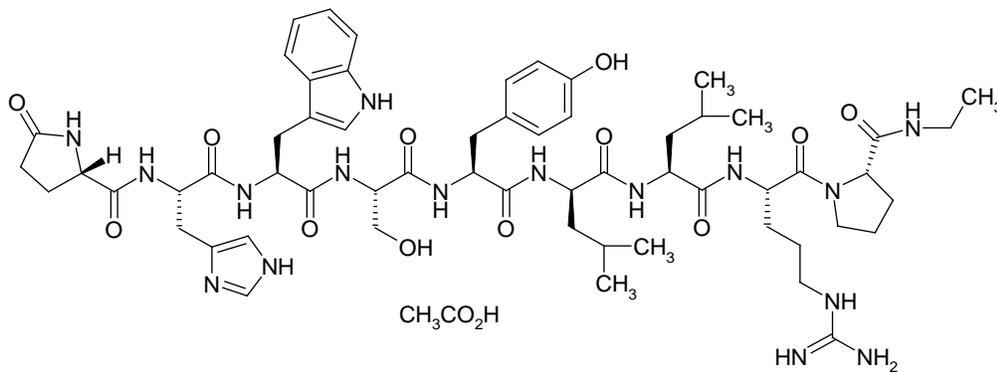
Proper name: Leuprolide acetate

Chemical name: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Molecular formula and molecular mass:  $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$ ,

1269.48 Daltons

Structural formula:



Physicochemical properties: Leuprolide acetate is a fine or fluffy, white to off-white powder. It is soluble in water, ethanol and propylene glycol with a pKa of 9.6.

## CLINICAL TRIALS

<b>Table 4: Summary of Patient Demographics for Open Label Clinical Trials with ELIGARD-administered SC to Patients with Prostate Cancer</b>		
<b>Dosage, route of administration and duration</b>	<b>Study subjects (n=number) Jewett Stage</b>	<b>Mean Age (Range)</b>
<b>ELIGARD 7.5 mg (1-Month)</b>		
<b>ELIGARD 7.5 mg</b> , 6 consecutive doses at monthly intervals Study duration: 6 months	120 Males  Stage C 74% Stage D 26%	Mean age 72.8 Range 52-85
<b>ELIGARD 22.5 mg (3-Month)</b>		
<b>ELIGARD 22.5 mg</b> , 2 consecutive doses at 3-month interval Study duration: 6 months	117 Males  Stage A 2% Stage B 16% Stage C 51% Stage D 31%	Mean age: 73.1 ± 8.0 yrs. Range: 46-85 yrs.
<b>ELIGARD 30 mg (4-Month)</b>		
<b>ELIGARD 30 mg</b> , 2 consecutive doses at 4-month intervals Study duration: 8 months	90 Males  Stage A 2% Stage B 42% Stage C 18% Stage D 38%	Mean age 73.5 ± 7.1 yrs. Range 53-84 yrs.
<b>ELIGARD 45 mg (6-Month)</b>		
<b>ELIGARD 45 mg</b> , 2 consecutive doses at 6-month intervals Study duration: 12 months	111 Males  Stage A 4% Stage B 39% Stage C 17% Stage D 40%	Mean age: 73.2 ± 7.5 yrs Range: 50-86 yrs

### Study Results

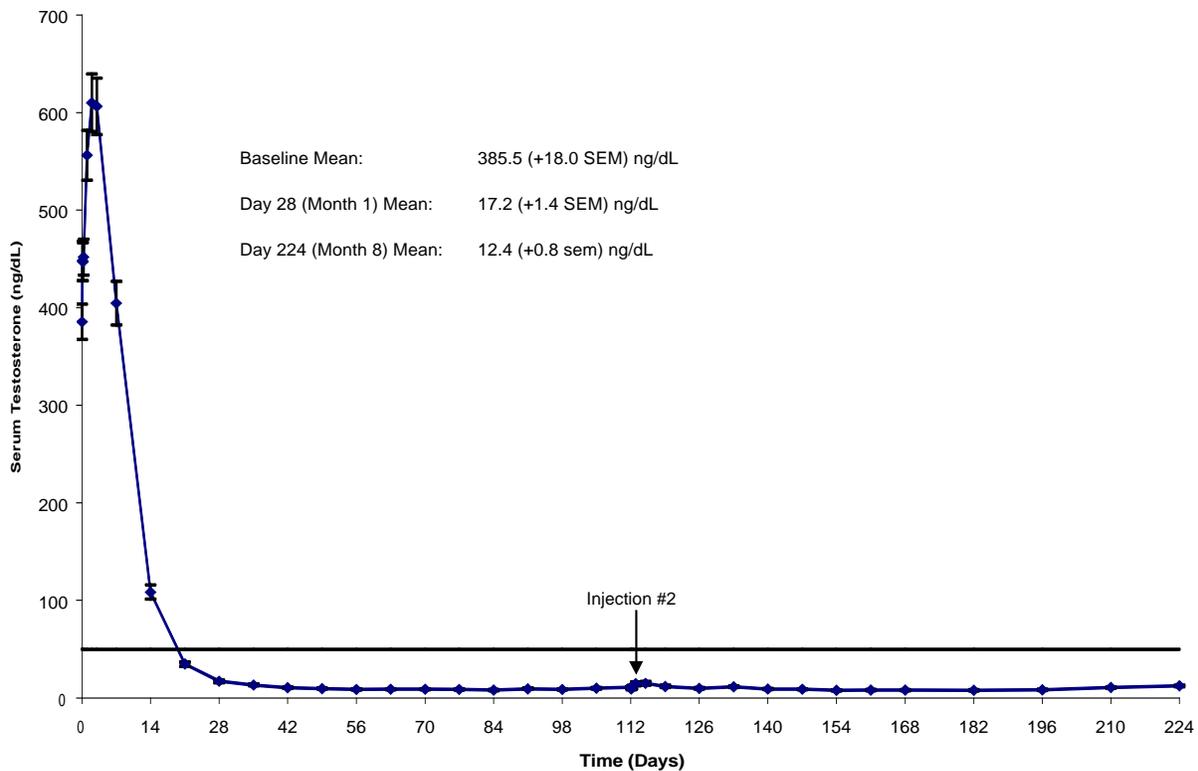
In the ELIGARD 7.5 mg (1-Month) phase III study 100% of patients who continued in the study through at least Day 14 reached castrate suppression of testosterone, defined as testosterone concentration of  $\leq 50$  ng/dL for two consecutive timepoints approximately one week apart. By Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and by Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all patients who achieved castrate testosterone suppression remained suppressed

throughout the duration of the study. Additionally, patient PSA scores were reduced by an average of greater than 90% from baseline during the study.

In the ELIGARD 22.5 mg (3-Month) phase III study, serum testosterone was suppressed to below the castrate threshold ( $\leq 50$  ng/dL) by Day 28 in all but one patient (99%). At Day 35, all patients (100%) who received a full dose at baseline attained castrate testosterone suppression. Once castrate testosterone suppression was achieved, only one (<1%) patient demonstrated breakthrough (concentrations above 50 ng/dL at anytime during the study after achieving castrate levels). This patient returned to castrate levels following his second injection and remained at castrate levels throughout the study. At the conclusion of the study (Month 6), all 111 evaluable patients (100%) had testosterone concentrations below castrate levels and 94% had achieved a threshold of  $\leq 20$  ng/dL. PSA scores were reduced 98% from baseline to Month 6.

The ELIGARD 30 mg (4-Month) clinical trial evaluated the achievement and maintenance of castrate serum testosterone suppression over eight months of therapy. A total of 82/90 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. By Month 8, the mean testosterone concentration was 12.4 ng/dL (Figure 27).

**Figure 27. ELIGARD 30 mg (4-Month) Mean Testosterone Concentrations (n = 90).**



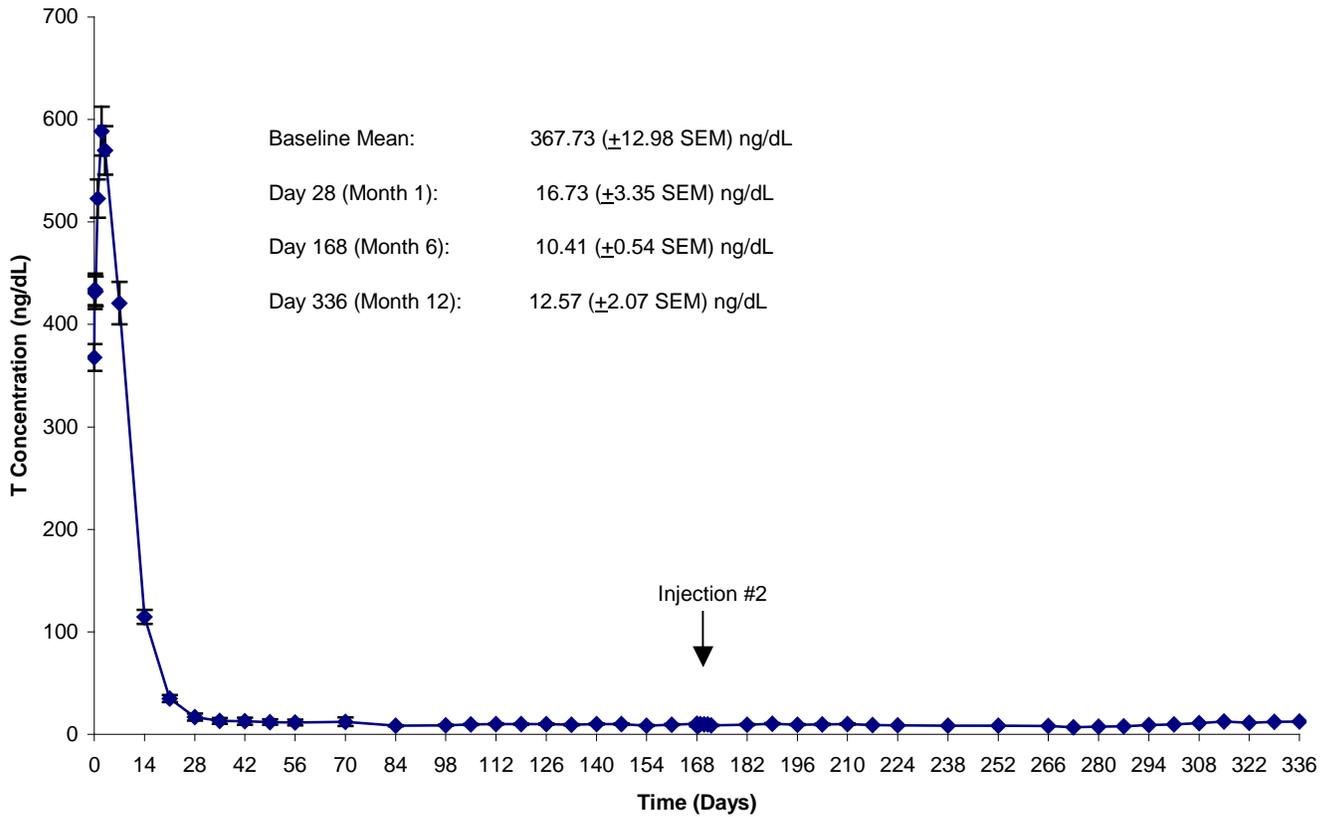
Of the original 90 patients, one voluntarily withdrew following the Day 14 visit, prior to achieving castrate suppression. Ninety-six percent (96%) of patients (85/89) reached castrate testosterone suppression levels ( $\leq 50$  ng/dL) by Month 1 (Day 28) following the baseline injection. All 89 (100%) of patients remaining in the study attained suppression by Day 42. A high proportion of patients (67% at Month 1 (Day 28), 90% at Day 42) achieved the more stringent criteria of testosterone suppression using a threshold of  $\leq 20$  ng/dL for at least two consecutive timepoints approximately one week apart. Three patients (3.3%) demonstrated breakthrough (concentration above 50 ng/dL) during the study, immediately following the second injection. All three patients subsequently resuppressed, and one of the three experienced a second breakthrough (53 ng/dL) by the end of Month 8. All other patients remaining in the study at Month 8 (n = 81) had testosterone concentrations of  $\leq 50$  ng/dL. Additionally, patient PSA score were reduced by an average of 86% from baseline during the study. At Month 8, PSA levels had decreased to within normal limits in 93% of the patients who presented with elevated levels at baseline.

Of the 111 patients in the ELIGARD 45 mg (6-Month) study 106 patients received a total of two injections of ELIGARD 45 mg given once every six months. A total of 103 patients completed the study. The mean 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. By Month-12, mean testosterone concentration was 12.6 ng/dL (Figure 28).

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%) 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 28: ELIGARD 45 mg (6-Month) Mean 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.

Summaries of WHO performance status, bone pain, urinary symptoms, and urinary pain all indicated good symptom control was maintained for the duration of each study (6 to 12 months) with no evidence of flare responses.

The observed safety profile of ELIGARD 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) and ELIGARD 45 mg (6-Month) was similar to that of other products containing leuprolide acetate.

### **Comparative Bioavailability Studies**

No comparative bioavailability studies were conducted between the various ELIGARD products.

## DETAILED PHARMACOLOGY

Leuprolide acetate is an analog of luteinizing hormone-releasing hormone. Following the administration of leuprolide acetate, there is an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). This causes a transient increase in levels of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate at therapeutic doses inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. As a result, testosterone is reduced in males to levels associated with castration ( $\leq 50$  ng/dL in serum), and estrogen in females is reduced to postmenopausal levels. These decreases are observed within two to four weeks after the start of treatment, and the effects are reversible upon discontinuation of drug therapy.

*Animal Pharmacology:* The pharmacological activity of ELIGARD (leuprolide acetate) was evaluated in mature male rats and dogs by measuring serum testosterone levels following dosing. These studies demonstrated that the product was effective in reducing the serum testosterone to  $\leq 50$  ng/dL, a value referred to in these studies as castrate levels.

After subcutaneous (SC) administration of ELIGARD 7.5 mg (1-Month) in a repeat-dose study in dog, testosterone levels decreased within seven days of initial dosing and were further reduced to castrate levels ( $\leq 50$  ng/dL) within 14 days. Castrate levels were maintained throughout the three-month study. Transient bursts in serum leuprolide acetate were observed for one to three days following each of the monthly injections. Between these bursts, leuprolide acetate levels remained low, but detectable. This study suggests that there was no accumulation of leuprolide acetate following repeat monthly SC injections of ELIGARD 7.5 mg (1-Month). Furthermore, no testosterone surge occurred as no increases in testosterone levels were detected following the second and third injections.

Serum testosterone levels were measured in male dogs following two injections of ELIGARD 22.5 mg (3-Month) administered 90 days apart. Castrate levels were achieved within two weeks after the first injection and were maintained for the duration of the 112-day study. No increase in testosterone was observed following the second injection at Day 91. Steady state levels of leuprolide were comparable to those following injections of LUPRON Depot<sup>®</sup> 22.5 mg.

In single-dose studies in rats and dogs, testosterone levels were suppressed to, or near castrate levels following administration of ELIGARD (bolus, SC) 7.5 mg (1-Month) and ELIGARD 22.5 mg (3-Month). As expected, testosterone levels increased immediately following administration of ELIGARD 7.5 mg (1-Month) and 22.5 mg (3-Month). Within two weeks of SC injection, levels of circulating testosterone decreased and remained below castrate level for the duration of the studies. A single bolus injection of ELIGARD 7.5 mg (1-Month) maintained testosterone suppression for five to six weeks in dogs and at least four weeks in rats. Thereafter, testosterone levels gradually increased and returned to pre-dosing levels within seven to eight weeks of dosing in both species. A single bolus injection of ELIGARD 22.5 mg (3-Month) maintained testosterone suppression for 91-133 days in rats and 84-91 days in dogs.

In a study conducted in rats, a single SC injection (12 mg/kg) of ELIGARD 30 mg (4-Month) produced serum testosterone suppression by Day 14 and maintained suppression through Day 132. The lower dose group (9 mg/kg) achieved a similar testosterone suppression, which was shown to persist until Day 105. Similar results were observed in a 156-day study in dogs in which a single SC injection of ELIGARD 30 mg (4-Month) produced continuous suppression of serum testosterone levels from Day 21 to Day 135 post-injection. These studies demonstrated that a 30 mg dose of leuprolide acetate in the ATRIGEL<sup>®</sup> formulation could achieve a four-month duration of activity in the absence of overt toxicity and injection site irritation in an animal model.

Studies in rats and dogs demonstrated that treatment with ELIGARD 45 mg suppresses serum testosterone to castrate levels for up to 196 days after one injection with minimal or no tissue irritation.

## **MICROBIOLOGY**

No microbiology studies were conducted with ELIGARD.

## **TOXICOLOGY**

### ***Acute Toxicology:***

Published studies on a sustained release formulation of leuprolide acetate demonstrated that the product has a low order of acute toxicity in mice and rats, with LD<sub>50</sub>'s above 5000 mg/kg (greater than 400 mg/kg of leuprolide acetate) for oral, subcutaneous and intraperitoneal routes of administration, and above 2000 mg/kg (greater than 160 mg/kg as leuprolide acetate) for intramuscular injection. The only clinical signs observed were related to local effects at the site of injection.

### ***Long-term Toxicity:***

In a four month repeat-dose study, rats were treated with ATRIGEL<sup>®</sup> Delivery System formulations containing 1, 3 or 10 mg/kg leuprolide acetate and ATRIGEL<sup>®</sup> Delivery System vehicle control (100 µL) subcutaneously twice per month for four months. Lupron Depot<sup>®</sup> 7.5 mg (10 mg leuprolide acetate/kg) was injected intramuscularly (IM) as a comparative control. Twenty-five animals (five per group) were terminated at 61 days and fifty animals were necropsied and a complete histopathological evaluation was performed on the animals treated with vehicle control, high-dose ELIGARD (10 mg/kg) and Lupron Depot<sup>®</sup> 7.5 mg.

Decreases in organ/ body weight ratios for the prostate, seminal vesicles, and testes at all termination intervals were noted in the test rats and were consistent with the known pharmacological activity of the drug. Localized injection site lesions such as bruising, excoriation, scabbing developed in some animals in all leuprolide/delivery system formulation groups and the delivery system vehicle controls. The bruises were more common after the first

and fourth injections and less frequent after the second and third injections in all affected groups. There was no similar localized injection site lesion after the fifth injection. This reaction appeared to be idiosyncratic and may have been related to procedural factors such as injection technique.

Hematology and clinical chemistry was not affected by treatment with ELIGARD and there were no remarkable behavioral changes reported in the treatment groups.

***Special Studies:***

To evaluate the irritation potential of ELIGARD 7.5 mg (1-Month), 0.25 mL of ELIGARD (bolus) was injected subcutaneously in mature, male beagle dogs once every 30 days for 3 consecutive injections. No clinical signs of toxicity or changes in body weight were noted during the study. Macroscopic and histologic examination revealed only mild to moderate local tissue reactions typical of a foreign body response.

The irritation potential of ELIGARD was also evaluated in rabbits injected once subcutaneously with 0.25 mL of ELIGARD (bolus or 2.3 mg leuprolide acetate/kg based on a 3.3 kg rabbit). Paired rabbits were sacrificed 7, 21, 28, and 56 days following treatment and the injection sites were examined histologically. Histological evaluation confirmed a foreign body reaction characterized by a mild to moderate irritant in comparison to a USP plastic negative control implant.

To further investigate the effect of ELIGARD at the site of injection, rats were treated with a single dose of ELIGARD (10 mg/kg leuprolide acetate, bolus by subcutaneous administration). Injection site reactions were observed in only 2 of 40 animals. Histological evaluation of the injection sites demonstrated a foreign body response, an effect that is consistent with the subcutaneous administration of an extended-release product.

In a rabbit implantation study, the local irritation potential of ELIGARD 22.5 mg (3-Month) SC was compared to an implanted USP plastic strip negative control. There was no overt toxicity and no macroscopic signs of irritation other than slight capsule formation ( $\leq 0.5$  mm) in 3 of 6 sites at Day 60. ELIGARD 22.5 (3-Month) was classed as a slight irritant at 7, 30, 90, 120 and 150 days post-dosing, and a nonirritant at 60 days post-dosing as compared to the USP negative control.

Two consecutive single subcutaneous injection of ELIGARD 22.5 mg (3-Month) (90 days apart) to dogs revealed no overt toxicity or body weight effects. Local irritation was absent to mild, with a slight foreign body response which decreased over time.

To investigate the effect of the ELIGARD 30 mg (4-Month) formulation at the site of injection, the local toxicity of the ELIGARD 30 mg (4-Month) formulation was evaluated in rats, dogs and pigs. Single doses of the formulation were administered subcutaneously to rats (12 mg/kg in 0.06 mL) and dogs (30 mg in 0.5 mL). In dogs, there were no overt toxicities, body weight abnormalities, or remarkable observations at the site of injection during a 28-day observation period after injection. In rats, no overt toxicity or injection site reactions were observed during

macroscopic tissue evaluation at necropsy on Day 105 and 132. In a dermal toxicity study, two pigs received eight simultaneous subcutaneous injections of four formulations, including two injections of the ELIGARD 30 mg (4-Month) formulation (2 X 0.5 mL). Overt toxicity and test site observations during the three-day observation period were unremarkable. The only treatment-related observation was minimal erythema at 6 of 8 injection sites in one animal.

Studies of 24 hours to 211 day duration in dogs and rats demonstrated that the ELIGARD 45 mg (6- Month) formulation is associated with no overt toxicity and produces minimal erythema and edema after subcutaneous injection. No overt toxicity or body weight abnormalities were observed in rats 24 hours after receiving a single subcutaneous dose (range: 6 mg to 45 mg leuprolide acetate) of ELIGARD 45 mg or a supporting formulation. Injection site irritation including redness and bruising was observed in studies where large volumes of formulation were injected (i.e., 0.25 - 0.5 mL). Macroscopic test site evaluations appeared more severe with increasing injection volume. Macroscopic evaluations including minimal to mild vasodilation, minimal to moderate erythema, and minimal to mild edema were observed with injection volumes of 0.375 to 0.5 mL.

A single SC injection (60 mg in 0.5 mL) of ELIGARD 45 mg or a supporting formulation in dogs showed no overt toxicities, no body weight abnormalities, and no remarkable observations at the injection sites during the study. In another study, dogs received a single SC injection (45 mg in 0.375 mL) of ELIGARD 45 mg or a supporting formulation. There were no body weight abnormalities during the study. Overt toxicity not related to the test article was observed in two dogs (i.e., seizures and otitis externa). Three dogs demonstrated minimal edema at the injection site on Day 1, and one dog had slight edema at the injection site on Day 14.

### ***Carcinogenicity***

Studies to determine the carcinogenic potential of ELIGARD have not been conducted. However, patients have been treated with leuprolide 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. Clinical signs of pituitary abnormalities have not been observed in any of these patients.

### ***Reproduction and Teratology***

Reproduction and teratology studies conducted with a sustained release formulation indicate all effects observed are related to consequences of repeated administration of this pharmacologic agent. Fertility studies, where male rats were dosed once every four weeks for three doses prior to mating, showed that the drug produced reversible atrophy of the testes or accessory sex organs at doses as low as 0.024 mg/kg (as leuprolide), and a decrease in LH, FSH and testosterone levels. A reversible decrease in copulation and implantation sites was also observed at the high dose of 2.4 mg/kg. No effects on the fetuses were observed.

Female rats dosed at 2.4 mg leuprolide acetate/kg once, four weeks prior to mating, caused an interruption in the estrus cycle and decreased vaginal size. Weights of the ovaries and uterus were decreased. Following mating, corpora lutea and the number of implantation sites were decreased at 0.24 mg/kg and above; the number of live fetuses was reduced at 2.4 mg/kg and above.

No abnormal development was noted in the fetuses. The sustained release formulation of leuprolide was not teratogenic in either rats or rabbits. In the perinatal study, the administration of the sustained release formulation of leuprolide prior to delivery at up to 8 mg/kg showed effects on sex organ weights, but no adverse effects on the fetuses, including weights of their sex organs.

***Mutagenicity***

A sustained release formulation of leuprolide was not mutagenic in either and *in vitro* cytogenetics assay using Chinese hamster lung cells or an *in vivo* micronucleus assay in mice.

In a study conducted to determine the ability of ELIGARD (leuprolide acetate 7.5 mg in an ATRIGEL<sup>®</sup> Delivery System) to induce mutations in five strains of *Salmonella typhimurium* (Ames test) the drug was found to be non-mutagenic.

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**PART III: CONSUMER INFORMATION**

**Pr<sup>®</sup>ELIGARD<sup>®</sup>  
Leuprolide acetate for injection  
Leuprolide acetate for injectable suspension**

**This leaflet is part III of a three-part "Product Monograph" published when ELIGARD was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ELIGARD. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION**

**What the medication is used for:**

- ELIGARD is prescribed for the palliative treatment of advanced prostate cancer (stage D2)

ELIGARD should be administered by a health care professional.

**What it does:**

ELIGARD is a member of a class of drugs known as luteinizing hormone-releasing hormone analogs, also called LH-RH analogs.

Leuprolide, the active medication inside ELIGARD, works by reducing testosterone, the natural male hormone produced by the testicles. Prostate cancer cells appear to need testosterone for their growth. When the body's supply of testosterone is lowered, prostate cancer usually shrinks or stops growing, which may result in a reduction of symptoms related to the disease.

**When it should not be used:**

- If you are allergic to any of the components of ELIGARD (see medicinal & nonmedicinal ingredient sections below) or if you have experienced prior allergic reaction including a severe allergic reaction (anaphylactic shock) to ELIGARD or other drugs like ELIGARD.
- ELIGARD should not be used in women who are or may become pregnant. ELIGARD may cause miscarriage or may cause harm to an unborn baby. ELIGARD is not recommended for use in breast-feeding women.

**What the medicinal ingredient is:**

Leuprolide acetate

**What the important nonmedicinal ingredients are:**

N-methyl-2-pyrrolidone  
Poly (DL-lactide-co-glycolide).

**What dosage forms it comes in:**

ELIGARD is supplied in two separate syringes. One syringe contains the active ingredient in a powder form. The other syringe is used to dilute the powder before use. The contents of the syringes are mixed just prior to administration.

ELIGARD 7.5 mg (1-Month): Injection once every one month (30 days)

ELIGARD 22.5 mg (3-Month): Injection once every 3 months.

ELIGARD 30 mg (4-Month): Injection once every 4 months.

ELIGARD 45 mg (6-Month): Injection once every 6 months.

ELIGARD works continuously and consistently over the time between injections.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

ELIGARD should be prescribed by a doctor experienced with this type of drugs.

ELIGARD may cause:

- Worsening of the symptoms of prostate cancer at the beginning of the treatment
- Pituitary apoplexy – bleeding or decreased blood flow causing tissue death of the pituitary gland.
- Bone thinning (osteoporosis)

Hormonal therapies for prostate cancer that reduce testosterone levels may lead to side effects such as loss of sexual desire and impotence. These symptoms have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism (inability of the testicle to produce testosterone and/ or sperm) will reverse in all patients has not yet been established.

ELIGARD is not indicated for use in women and children less than 12 years of age, as safety and efficacy have not been established in these groups of patients.

**BEFORE you use ELIGARD talk to your doctor or pharmacist if:**

- you are allergic to the drug leuprolide acetate
- you are taking prescription or non-prescription drugs
- you have a history of urinary tract obstruction
- you have had spread of cancer to the bones of the spine (vertebrae) or have a history of spinal cord compression
- you have low red blood cell count (anemia)
- you have family history of severe osteoporosis, have low bone mineral density, if you are taking any medication that can cause thinning of the bones (such as corticosteroids or anti-convulsive (anti-seizure) medication), or if you use alcohol or tobacco. ELIGARD may increase your risk of bone thinning (osteoporosis) and bone fractures.
- you have heart disease, or a genetic heart condition called “Long QT syndrome”
- you have diabetes (high blood sugar). ELIGARD may affect your blood glucose level and you may need to test you blood sugar more frequently while taking ELIGARD.

**INTERACTIONS WITH THIS MEDICATION**

Talk to your doctor or pharmacists if you take any other medication or before using any other medication.

Drugs that may interact with ELIGARD include, but are not limited to:

- antiarrhythmic drugs (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antipsychotic drugs (used to treat mental disorders) such as: chlorpromazine
- antidepressant drugs (used to treat depression) such as: amitriptyline, nortriptyline
- opioid drugs, such as methadone
- antibiotics, such as: erythromycin, clarithromycin, azithromycin, moxifloxacin
- antifungals
- antimalarials, such as quinine
- drugs belonging to a class called beta-2 agonists, such as salbutamol
- drugs belonging to a class called 5-HT3 antagonists, such as ondansetron

**PROPER USE OF THIS MEDICATION**

Usual dose:

ELIGARD is an injection that gives you and your physician the convenient choice of four dosage forms: once every 6 months (45 mg), once every 4 months (30 mg), once every 3 months (22.5 mg), or once monthly (7.5 mg).

If your situation changes, you and your doctor may need to re-evaluate your treatment regimen. Your doctor can help you decide which ELIGARD regimen is best for you.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is very important that you keep all scheduled appointments with your doctor. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of ELIGARD injections is an important part of treatment. Maintaining testosterone suppression is a key element in treating the symptoms of hormone-dependent prostate cancer.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

- Occasionally, you may experience a local skin reaction: burning and stinging, pain, redness, itching and/or swelling at the injection site. These reactions usually are mild and resolve after a few days. If they persist or become irritating, contact your physician.
- You may experience hot flashes during your treatment. If they continue and make you feel uncomfortable, contact your physician.
- Contact your physician immediately if you experience any of the following symptoms: severe bone pain, severe hot flashes, heavy sweating, severe pain in the chest or abdomen, abnormal swelling, numbness/ weakness or paralysis of lower limbs, persistent nausea or vomiting, lightheadedness or dizziness,

persistent sad mood, rapid heart beat, nervousness or persistent difficulty in urinating.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Itching, redness, burning and/or swelling at injection site	√		
	hot flashes	√		
	lightheadedness or dizziness		√	
Uncommon	severe bone pain		√	
	heavy sweating		√	
	pain in the chest or abdomen		√	
	abnormal swelling		√	
	numbness of limbs		√	
	persistent nausea or vomiting		√	
	rapid heart beat		√	
	nervousness		√	
	persistent sad mood		√	
persistent difficulty in urinating		√		

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown frequency	Sudden headache, vomiting, visual changes, impaired consciousness		√	
	Allergic reactions, with symptoms such as: shortness of breath, redness, itching, low blood pressure, fainting			√
	Convulsions		√	
	Respiratory symptoms such as shortness of breath at rest or aggravated by effort, dry cough			√

*This is not a complete list of side effects. For any unexpected effects while taking ELIGARD, contact your doctor or pharmacist.*

**HOW TO STORE IT**

ELIGARD should be kept refrigerated between 2-8°C (36-46°F).

ELIGARD can be stored at room temperature (15 – 30 °C) in original packaging for a period of 8 weeks prior to administration.

Once mixed, ELIGARD should be discarded if not used within 30 minutes.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: [www.sanofi.ca](http://www.sanofi.ca) or by contacting the sponsor at: 1-800-265-7927

This leaflet was prepared by sanofi-aventis Canada Inc.

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