PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ELIGARD®

Leuprolide acetate for extended-release injectable suspension

Powder, 7.5 mg [1-Month], 22.5 mg [3-Month], 30 mg [4-Month] and 45 mg [6-Month],

for subcutaneous use

Luteinizing Hormone-Releasing Hormone Analog

DIN Holder:
Tolmar International Ltd.
Dublin 2, Ireland D02 T380

Imported by:
Innomar Strategies Inc.
Oakville, ON L6L 0C4
Canada

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RECENT MAJOR LABEL CHANGES

1 Indications	09/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Prostate Cancer

ELIGARD 7.5 mg (1-month), 22.5 mg (3-month), 30 mg (4-month) and 45 mg (6-month) are indicated for the treatment of advanced prostate cancer.

Central Precocious Puberty (CPP)

ELIGARD 45 mg (6-month) is indicated for the treatment of children 2 years of age and older with central precocious puberty (CPP).

1.1 Pediatrics

Pediatrics (≥ 2 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ELIGARD 45 mg in pediatric patients has been established for the treatment of Central Precocious Puberty; therefore, Health Canada has authorized an indication for patients 2 years of age and older (see 14 CLINICAL TRIALS). The safety and effectiveness of Eligard have not been established in pediatric patients less than 2 years old.

1.2 Geriatrics

Geriatrics (≥ 70 years of age): The majority (> 70%) of the patients studied in the clinical trials for the treatment of advanced prostate cancer with ELIGARD were 70 years and older (see 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

ELIGARD is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. 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 section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- females 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 females is not recommended (see 7.1 Special Populations and 16 NON-CLINICAL TOXICOLOGY).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Prostate Cancer

The following are clinically significant adverse events:

- Clinical testosterone flare reaction in men with prostate cancer (see 7 WARNINGS AND PRECAUTIONS, General).
- Pituitary apoplexy (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).
- Osteoporosis (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

ELIGARD should be prescribed by a qualified physician experienced in the use of hormonal therapy. ELIGARD must be administered by a healthcare professional.

Prostate Cancer

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.

Central Precocious Puberty

ELIGARD 45 mg, administered subcutaneously once every 6 months, is designed to provide continuous sustained release of leuprolide. Discontinue ELIGARD treatment at the appropriate age of onset of puberty. ELIGARD does not require a dose adjustment based on patient weight.

Monitor response to ELIGARD with a GnRH agonist stimulation test, basal serum luteinizing hormone (LH) levels or serum concentration of sex steroid levels at 1 to 2 months following initiation of therapy and as needed to confirm adequate suppression of pituitary gonadotropins, sex steroids, and progression of secondary sexual characteristics. Measure height (for calculation of growth velocity) every 3 to 6 months and monitor bone age periodically. If the therapeutic response is not adequate, consider switching to an alternative therapy.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of each strength of ELIGARD is shown in Table 1. Each dose is administered as a single subcutaneous injection after reconstituting with a special polymer formulation (see 4.4 Administration).

Table 1. Recommended Dose of ELIGARD

Strength	Dose Schedule	Total Injection Weight	Amount of Leuprolide Acetate	Total Injection Volume
Prostate Cancer				
7.5 mg	Monthly (every 4 weeks)	250 mg	7.5 mg	0.25 mL
22.5 mg	Every 3 months (every 12 weeks)	375 mg	22.5 mg	0.375 mL
30 mg	Every 4 months (every 16 weeks)	500 mg	30 mg	0.50 mL
Prostate Cancer and Central Precocious Puberty				
45 mg	Every 6 months (every 24 weeks)	375 mg	45 mg	0.375 mL

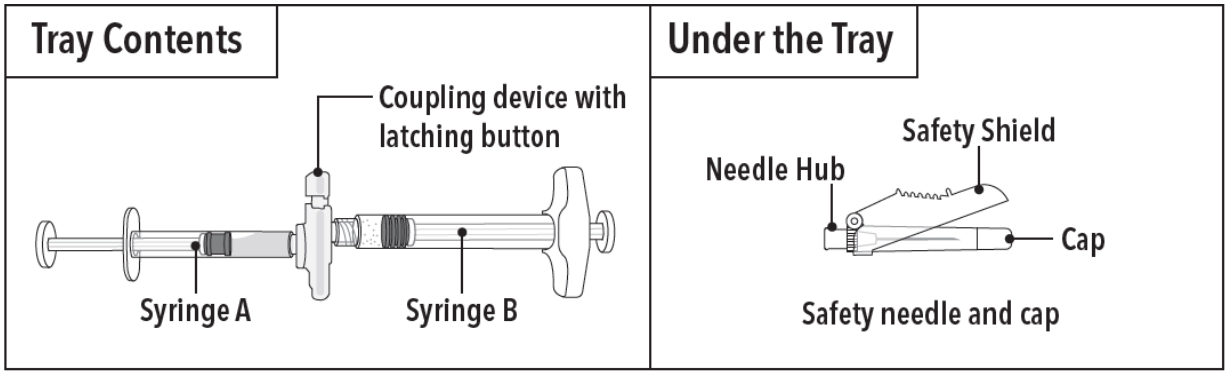
4.3 Reconstitution

ELIGARD is packaged in a carton containing:

- Tray containing a pre-connected syringe system with desiccant pack
- Package insert
- Sterile safety needle and cap, provided under tray

Tray Packaging

Figure 1. Eligard Tray Contents



Follow the instructions as directed to ensure proper preparation of ELIGARD prior to administration. For more detailed instructions, see INSTRUCTIONS FOR USE. If the product is not prepared using the proper technique, it should not be administered, as lack of clinical efficacy may occur.

IMPORTANT:

- Use aseptic technique throughout the procedure.
- As with other similar agents, the use of gloves is recommended during mixing and administration.
- Allow the product to reach room temperature by removing it from the refrigerator at least 30 minutes before mixing. Note, before reconstitution, ELIGARD can be stored at room temperature (15 – 30°C) in original packaging for a period of 8 weeks prior to administration (see 11 STORAGE, STABILITY AND DISPOSAL).

- Once mixed, the product must be administered within 30 minutes or it should be discarded. The viscosity of the solution (or suspension) increases with time.
- ONLY use ATRIGEL®[1] Delivery System to reconstitute the product, in order to ensure providing the continuous sustained release of the product.

1. On a clean field open the tray by tearing off the foil from the corner and remove the contents. Discard the desiccant pack. Remove the pre-connected syringe system from the tray. Open the sterile safety needle package by peeling back the paper tab. **Note:** Syringe A and Syringe B should not be lined-up yet.

   The product should only be administered with the co-packaged, sterile safety needle.

2. Grasp the latching button on the coupling device with your finger and thumb and press until you hear a snapping sound. The two syringes will be aligned.

   Do not bend the pre-connected syringe system.

3. Holding the syringes in a horizontal position, initially transfer the liquid contents of Syringe A into the leuprolide acetate powder contained in Syringe B. **Thoroughly mix the product for 60 cycles by pushing the contents back and forth between both syringes to obtain a homogenous, viscous suspension.**

   - **A full cycle is one push of the Syringe A plunger and one push of the Syringe B plunger.**
   - When thoroughly mixed, the viscous suspension will appear light tan to tan (ELIGARD 7.5 mg) or colorless to pale yellow (ELIGARD 22.5 mg, 30 mg, and 45 mg).

   Note: Product must be mixed as described; shaking will NOT provide adequate mixing. Do not bend.

4. After mixing, hold the syringes vertically (upright) with Syringe B (wide syringe) on the bottom. The syringes should remain securely coupled. Transfer all of the mixed product into Syringe B by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger.

5. While ensuring the Syringe A plunger is fully pushed down, hold the coupling device and unscrew Syringe B. This will disconnect Syringe B from the coupling device. Syringe A will remain attached to the coupling device.

   Note: Small air bubbles will remain in the formulation – this is acceptable.

   Do not purge the air bubbles from Syringe B as product may be lost.

[1] ATRIGEL® is a registered trademark of Tolmar, Inc.

6. Continue to hold Syringe B upright with the open end at the top. Hold back the white plunger on Syringe B to prevent loss of the product and attach the safety needle and cap. Gently screw clockwise with approximately a three-quarter turn until the safety needle and cap are secure.

   Do not overtighten, as the needle hub may become damaged which could result in leakage of the product during injection. The safety shield may also be damaged if the safety needle and cap are screwed with too much force.

7. Move the safety shield away from the needle and towards the syringe.

   Pull off the cap immediately prior to administration.

Note: Should the needle hub appear to be damaged, or leak, the product should NOT be used. The damaged safety needle and cap should NOT be replaced and the product should NOT be injected. In the event of damage to the needle hub, use a new replacement ELIGARD carton.

4.4 Administration

As with all parenteral drug products, syringes as well as reconstituted drug solutions (or suspensions), visually inspect before use. Do not use if particulate matter, precipitate, discolouration or leakage is present. Solutions (or suspensions) showing particulate matter, precipitate, discolouration or leakage should not be used.

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

Administration procedure (for more detailed instructions, see INSTRUCTIONS FOR USE):

1. Select an injection site on the abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair and hasn't recently been used.

2. Cleanse the injection-site area with an alcohol swab (not enclosed).

3. Using the thumb and forefinger, grab and bunch the area of skin around the injection site.

4. Using your dominant hand, insert the needle quickly at a 90° angle to the skin surface. The depth of penetration will depend on the amount and fullness of the subcutaneous tissue and the length of the needle. After the needle is inserted, release the skin.

5. Inject the drug using a slow, steady push and press down on the plunger until the syringe is empty.

   Make sure all the drug has been injected before removing the needle.

6. Withdraw the needle quickly at the same 90° angle used for insertion.

7. Immediately following the withdrawal of the needle, activate the safety shield using a finger/thumb or flat surface and push until it completely covers the needle tip and locks into place.

8. An audible and tactile “click” verifies a locked position.

9. Check to confirm the safety shield is fully engaged. Discard all components safely in an appropriate biohazard container.

4.5 Missed Dose

Adherence to drug administration schedules is important to ensure the efficacy of gonadotropin releasing hormone agonist over the full dosing schedule. For central precocious puberty, noncompliance with drug regimen may lead to gonadotropins and/or sex steroids increasing above prepubertal levels resulting in inadequate control of the pubertal process. 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.

5 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 received leuprolide acetate subcutaneously at a dose of either 1 or 10 mg/day for up to three years or 20 mg/day for up to two years.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

ELIGARD is an injectable suspension of leuprolide acetate available in a pre-connected syringe system and packaged with a sterile safety needle and cap (Figure 1), a desiccant, and a package insert with instructions for use. The pre-connected syringe system consists of syringe A and syringe B connected using a coupling device. Syringe A contains the ATRIGEL® Delivery System [poly (DL-lactide-co-glycolide) and N-methyl-2-pyrrolidone] that is light tan to tan, clear viscous solution (ELIGARD 7.5 mg) or colourless to pale yellow, clear viscous solution (ELIGARD 22.5 mg, 30 mg and 45mg). Syringe B contains leuprolide acetate that is white to off-white powder.

When reconstituted, ELIGARD is administered as a single dose. The ATRIGEL® Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, poly (DL-Lactide-co-glycolide) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (Table 2).

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength	Non-Medicinal Ingredients
Subcutaneous Injection	7.5 mg (1-Month) leuprolide acetate for extended-release injectable suspension	50:50 Poly (DL-Lactide-co-glycolide)*, N-methyl-2-pyrrolidone
	22.5 mg (3-Month) leuprolide acetate for extended-release injectable suspension	75:25 Poly (DL-Lactide-co-glycolide)*, N-methyl-2-pyrrolidone

	30 mg (4-Month) leuprolide acetate for extended-release injectable suspension	75:25 Poly (DL-Lactide-co-glycolide)*, N-methyl-2-pyrrolidone
	45 mg (6-Month) leuprolide acetate for extended-release injectable suspension	85:15 Poly (DL-Lactide-co-glycolide)*, N-methyl-2-pyrrolidone

** Co-polymer molar ratio of DL-lactide to glycolide containing carboxyl end groups.*

Carton Contents
ELIGARD 7.5, 22.5, 30 and 45 mg is packaged in one thermoformed tray placed into a paperboard carton. The ELIGARD carton contains: • Tray containing pre-connected syringe system (syringe A is pre filled with the ATRIGEL® Delivery System and syringe B is filled with leuprolide acetate powder) and desiccant pack. • Package insert. • One 20-gauge 5/8 inch sterile safety needle and cap (7.5, 22.5 and 30 mg) or one 18-gauge 5/8 inch sterile safety needle and cap (45 mg), provided under tray. •

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

All Indications

General

Mixing and administration procedures should be followed, as lack of clinical efficacy may occur due to incorrect reconstitution or administration of the product (see 4.4 Administration and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Carcinogenesis and Mutagenesis

No carcinogenicity studies or genotoxicity studies have been conducted specifically with ELIGARD.

There is no evidence of carcinogenic or mutagenic effects with the use of ELIGARD in humans.

A two-year carcinogenicity study conducted with leuprolide acetate in rats found increased incidences of benign pituitary hyperplasia, benign pituitary adenomas, pancreatic islet-cell adenomas, and testicular interstitial cell adenomas (see 16 NON-CLINICAL TOXICOLOGY). Patients with advanced prostate cancer have been treated with leuprolide acetate for up to two years with doses as high as 20 mg/day and up to three years with doses as high as 10 mg/day without demonstrable pituitary abnormalities.

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

Changes in Bone Density

Decreased bone mineral density can be anticipated with long-term use of an LHRH agonist. Bone density may decrease with GnRH agonist in children with central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

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, monitoring 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, physicians should carefully consider whether the benefits of androgen deprivation therapy outweigh the risks of changes in bone density 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 upon discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Neurologic

Convulsions

Postmarketing reports of convulsions have been observed in adult and pediatric patients receiving GnRH agonists, including leuprolide acetate. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and selective-serotonin-reuptake inhibitors (SSRIs). Convulsions have also been reported in patients in the absence of any of the conditions mentioned above (8 ADVERSE REACTIONS).

Idiopathic Intracranial Hypertension (pseudotumor cerebri)

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in adult and pediatric patients receiving GnRH agonists, including leuprolide acetate. Monitor patients for signs and symptoms of idiopathic intracranial hypertension, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. Treatment should be discontinued immediately if the patient develops any signs or symptoms suggestive of idiopathic intracranial hypertension.

Reproductive Health: Female and Male Potential

- **Fertility**
  Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with ELIGARD. Clinical and pharmacologic studies in adults (> 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility

suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks (see 10 CLINICAL PHARMACOLOGY).

There is no evidence that pregnancy rates are affected following discontinuation of ELIGARD. Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression (see 16 NON-CLINICAL TOXICOLOGY).

- **Function**
  Hormonal therapies for prostate cancer that reduce testosterone levels may lead to side effects such as loss of sexual desire and erectile dysfunction.
- **Teratogenic Risk**
  ELIGARD is contraindicated in females who are or may become pregnant (see 2 CONTRAINDICATIONS). Exclude pregnancy in females of reproductive potential prior to initiating ELIGARD, as ELIGARD may cause embryo-fetal harm when administered during pregnancy (see 7.1 Special Populations, 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

  ELIGARD is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a nonhormonal method of contraception during treatment with ELIGARD.

Prostate Cancer

General

ELIGARD, like other LH-RH analogs, causes a transient increase in serum concentration of testosterone during the first two weeks of treatment, known as a testosterone flare reaction. 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 observed 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 acetate therapy under close supervision.

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. 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, monitoring and management according to clinical practice and guidelines should be considered (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Effect on QT/QTc Interval

Androgen deprivation therapy has the potential to prolong QT/QTc interval on electrocardiogram (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 (see 9.2 Drug Interactions Overview and 10.2 Pharmacodynamics).

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.

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 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Diabetic patients may require more frequent monitoring when receiving LH-RH agonists. Assessment of glucose tolerance, monitoring and management according to clinical practice and guidelines should be considered.

Hematologic

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

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.

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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Response to ELIGARD may be monitored by periodically measuring serum concentrations of testosterone and prostate specific antigen (PSA). 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 the case of suspected or known handling errors, as lack of efficacy may result from incorrect preparation or administration.

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

The effects of leuprolide acetate 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.

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.

Central Precocious Puberty

General

Initial Rise of Gonadotropins and Sex Steroid Levels

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug (see 10 CLINICAL PHARMACOLOGY). Therefore, an increase in clinical signs and symptoms of puberty including vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses (see 8 ADVERSE REACTIONS). Instruct patients and caregivers to notify the physician if these symptoms continue beyond the second month after ELIGARD administration.

Psychiatric

Psychiatric events have been reported in pediatric patients taking GnRH agonists, including leuprolide acetate. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with ELIGARD (see 8 ADVERSE REACTIONS). Call your child's doctor right away if your child has any new or worsening emotional symptoms while taking ELIGARD.

Monitoring and Laboratory Tests

See 4 DOSAGE AND ADMINISTRATION, Dosing Considerations.

7.1 Special Populations

7.1.1 Pregnant Women

Eligard is contraindicated during pregnancy or in females who may become pregnant (see 2 CONTRAINDICATIONS). Eligard may cause fetal harm based on findings from animal studies and the drug's mechanism of action (see 10 CLINICAL PHARMACOLOGY). The available data from published clinical studies and case reports and from the pharmacovigilance database on exposure to leuprolide acetate during pregnancy are insufficient to assess the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on animal reproduction studies, leuprolide acetate may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. If a patient becomes pregnant during treatment, she should stop taking Eligard and consult her physician.

7.1.2 Breast-Feeding

There are no data on the presence of leuprolide acetate in either animal or human milk, the effects on the breastfed infants, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ELIGARD and any potential adverse reactions on the breastfed infant from ELIGARD or from the underlying maternal condition. The use of ELIGARD in nursing females is not recommended.

7.1.3 Pediatrics

The safety and effectiveness of ELIGARD have not been established in pediatric patients less than 2 years old.

7.1.4 Geriatrics

Geriatrics (≥ 70 years of age): The majority (> 70%) of the patients studied in the clinical trials for the treatment of advanced prostate cancer with ELIGARD were 70 years and older (see 14 CLINICAL TRIALS). No overall differences in safety or effectiveness of ELIGARD were observed between elderly and younger patients with advanced prostate cancer.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

8.1.1 Prostate Cancer

The safety of all ELIGARD formulations was evaluated in clinical trials involving patients with advanced prostate cancer. The safety of ELIGARD 7.5 mg (1-Month) was evaluated in 128 patients with advanced prostate cancer (N = 8 orchiectomized and N = 120 non-orchiectomized). The safety of ELIGARD 22.5 mg (3 Month), 30 mg (4-Month) and ELIGARD 45 mg (6-Month) was evaluated in 117, 90 and 111 non-orchiectomized patients with advanced prostate cancer, respectively. ELIGARD caused a transient increase in serum testosterone concentrations during the first 2 weeks of treatment.

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 related to its pharmacological action of sex hormone suppression.

Local adverse events reported in ≥ 5% of patients after injection of all doses of ELIGARD included transient burning and stinging (27.5% 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.

8.1.2 Central Precocious Puberty

The following serious adverse reactions are described here and in 7 WARNINGS AND PRECAUTIONS.

- Initial rise in gonadotropin and sex steroid levels
- Psychiatric Events
- Convulsions
- Idiopathic Intracranial Hypertension (pseudotumor cerebri)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

Prostate Cancer

Five clinical studies (AGL9904, AGL9802, AGL9909, AGL0001 and AGL0205) of ELIGARD were conducted in males with advanced prostate cancer. These open label, uncontrolled studies ranged from 6 months to 1 year in duration. The average age of patients across the studies was 73 years old (refer to Table 7 and Table 8 for additional study details). The following (Table 3) possibly or probably related systemic adverse events were reported by ≥ 5% of the patients administered ELIGARD 7.5 mg, 22.5 mg, 30 mg and 45 mg in clinical studies.

Table 3. Summary of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 5% of Patients Treated with ELIGARD

ELIGARD® Dose		7.5 mg	7.5 mg	22.5 mg	30 mg	45 mg
Study Number		AGL9904	AGL9802	AGL9909	AGL0001	AGL0205
Number of Patients		120	8	117	90	111
Treatment		1 injection every month up to 6 months	1 injection (surgically castrated patients)	1 injection every 3 months up to 6 months	1 injection every 4 months up to 8 months	1 injection every 6 months up to 12 months
MedDRA System Organ Class[6]	Adverse Event	Number (percent)				
General Disorders and Administration Site Conditions	Fatigue	15 (12.5%)	-	8 (6.8%)	12 (13.3%)	11 (9.9%)
Reproductive System and Breast Disorders	Testicular atrophy[5]	6 (5.0%)	-	-	-	8 (7.2%)
Vascular Disorders	Hot Flush[5]	67 (55.8%)[1]	2 (25.0%)[1]	66 (56.4%)[2]	66 (73.3%)[3]	64 (57.7%)[4]

1. A total of 86 hot flushes/sweats adverse events were reported in 70 patients. Of these, 71 events (83%) were mild; 14 (16%) were moderate; 1 (1%) was severe.
2. A total of 84 hot flushes/sweats adverse events were reported in 66 patients. Of these, 73 events (87%) were mild; 11 (13%) were moderate; none were severe.
3. A total of 75 hot flush adverse events were reported in 66 patients. Of these, 57 events (76%) were mild; 16 (21%) were moderate; 2 (3%) were severe.
4. A total of 89 hot flush adverse events were reported in 64 patients. Of these, 62 events (70%) were mild; 27 (30%) were moderate; none were severe.
5. Expected pharmacological consequences of testosterone suppression.
6. All data updated to conform with MedDRA version 24.1.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

ELIGARD was evaluated in an uncontrolled, open-label, clinical trial in which 64 pediatric patients with CPP received at least one dose of ELIGARD. The age ranged from 4 to 9 years at start of treatment; 62 patients were female and 2 were male; 53% White; 23% Black; 8% American Indian or Alaska Native; 5% Asian; 2% Native Hawaiian or Other Pacific Islander. 56% of the subjects self-identified as Hispanic or Latino ethnicity. There were no adverse events that led to withdrawal from the study or discontinuation of study drug. Adverse reactions that occurred in ≥ 5% of patients are shown in Table 4.

Table 4. Adverse Reactions Occurring in ≥ 5% of Patients Treated with ELIGARD 45 mg in an Open-Label, Trial (TOL2581A) for Central Precocious Puberty

Adverse Event	% of Patients (N=64)
Injection site pain[1]	31
Nasopharyngitis	22
Pyrexia	17
Headache	16
Cough	13
Abdominal pain	9

Adverse Event	% of Patients (N=64)
Injection site erythema[1]	9
Nausea	8
Constipation[1]	6
Vomiting	6
Upper respiratory tract infection[1]	6
Bronchospasm[1]	6
Productive cough[1]	6
Hot flush[1]	5
Bronchitis[1]	5
Pharyngitis[1]	5
Pharyngitis streptococcal[1]	5
Sinusitis[1]	5

1. All occurrences were reported as Grade 1.

8.3 Less Common Clinical Trial Adverse Reactions

Prostate Cancer

The following possibly or probably related systemic adverse events were reported by < 5% of patients administered ELIGARD 7.5 mg (1-Month), 22.5 mg (3-Month), 30 mg (4-Month) or 45 mg (6-Month) in clinical studies.

Blood and Lymphatic System Disorders:	decreased red blood cell count, hematocrit and hemoglobin (anemia)
Gastrointestinal Disorders:	dry mouth, nausea, stomach upset, flatulence, constipation, diarrhea, gastroenteritis/colitis
General Disorders and Administration Site Conditions:	fever, malaise, rigors, weakness, lethargy, pain (not otherwise specified), erythema[2], bruising[2], pruritis[2], induration[2], ulceration[2]
Metabolism and Nutrition Disorders:	weight gain
Musculoskeletal and Connective Tissue Disorders:	myalgia, muscle atrophy, arthralgia, backache, joint pain, limb pain, tremor
Nervous System Disorders:	disturbance of smell and taste, vertigo, dizziness, syncope
Psychiatric Disorders:	insomnia, depression, libido decreased[1]
Renal and Urinary Disorders:	urinary urgency, urinary frequency, incontinence, nocturia, aggravated nocturia, difficulties with urination, urinary retention, pain on urination, scanty urination, bladder spasm, and blood in urine
Reproductive System and Breast Disorders:	breast tenderness, gynecomastia, testicular atrophy[1] and soreness/pain, reduced penis size[1], penile disorder[1], erectile dysfunction[1], impotence[1]

Skin and Subcutaneous Tissue Disorders:	clamminess, sweating, night sweats, alopecia
Vascular Disorders:	hypertension, hypotension, vasodilation

1. Expected pharmacological consequence of testosterone suppression.
2. These events were mostly reported as mild and generally resolved within a few days post injection.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Central Precocious Puberty

The following possibly or probably related systemic adverse events were reported by < 5% of patients administered ELIGARD 45 mg (6-Month) in clinical studies.

Psychiatric Disorders: emotional disorder (2%), irritability (2%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Prostate Cancer

Abnormalities of certain parameters were observed but are difficult to assess in this population and in relation to the drug treatment.

Across all ELIGARD dose strengths, clinical chemistry laboratory values of CTCAE Grade 1-2 observed in ≥ 10% of the study population at any time during the ELIGARD clinical studies included: increased alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), bilirubin, total cholesterol, creatine kinase (CK), creatinine, lactate dehydrogenase (LDH), sodium and triglycerides.

Hematology laboratory values of CTCAE Grade 1-2 observed in ≥ 5% of the study population at any time during the clinical studies included: increased eosinophils and International Normalized Ratio (INR); decreased erythrocytes, lymphocytes, neutrophils and hemoglobin.

CTCAE Grade 3 laboratory abnormalities observed in ≥ 5% of the study population at any time during the ELIGARD clinical studies included: increased triglycerides, CK and INR and decreased lymphocytes. CTCAE Grade 4 abnormalities observed in ≤ 5% of the ELIGARD study populations included: increased CK (3.3%), potassium (1%) and triglycerides (1%), and decreased sodium (1%) lymphocytes (1%), and neutrophils (2%).

Central Precocious Puberty

There were no clinically significant laboratory abnormalities in pediatric patients in study TOL2581A.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-marketing use of leuprolide acetate or ELIGARD. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

All Indications

Nervous System Disorders: convulsion, idiopathic intracranial hypertension (pseudotumor cerebri) (see 7 WARNINGS AND PRECAUTIONS, Neurologic)

Prostate Cancer

Endocrine Disorders: pituitary apoplexy (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

Immune System Disorders: anaphylactic/anaphylactoid reactions including anaphylactic shock (see 2 CONTRAINDICATIONS)

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

Central Precocious Puberty

Immune System Disorders: anaphylactic, rash, urticaria, and photosensitivity reactions.

General Disorders and Administration Site Conditions: chest pain, weight increase, weight decrease, decreased appetite, fatigue.

Investigations: decreased white blood cells.

Metabolism and Nutrition Disorders: diabetes mellitus.

Musculoskeletal and Connective Tissue Disorders: arthralgia, epiphysiolysis, muscle spasms, myalgia.

Nervous System Disorders: neuropathy peripheral, paralysis, insomnia.

Psychiatric Disorders: emotional lability, such as crying, irritability, impatience, anger and aggression. Depression, including rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Skin and Subcutaneous Tissue Disorders: injection site reactions including induration and abscess, flushing, hyperhidrosis.

Reproductive System and Breast Disorders: vaginal bleeding, breast enlargement.

Vascular Disorders: hypertension, hypotension.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Androgen deprivation treatment may prolong the QTc interval, thus, 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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). 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-HT3) receptor antagonists (e.g., ondansetron), and beta-2 adrenoceptor agonists (e.g., salbutamol).

9.3 Drug-Behavioural Interactions

No data are available on the interaction of leuprolide with alcohol.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Therapy with leuprolide acetate results in suppression of the hypothalamic pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide acetate therapy may be affected.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring luteinizing hormone-releasing hormone (LH-RH) that, when administered continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. The analog possesses greater potency than the natural hormone. Leuprolide 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.

10.2 Pharmacodynamics

10.2.1 Prostate Cancer

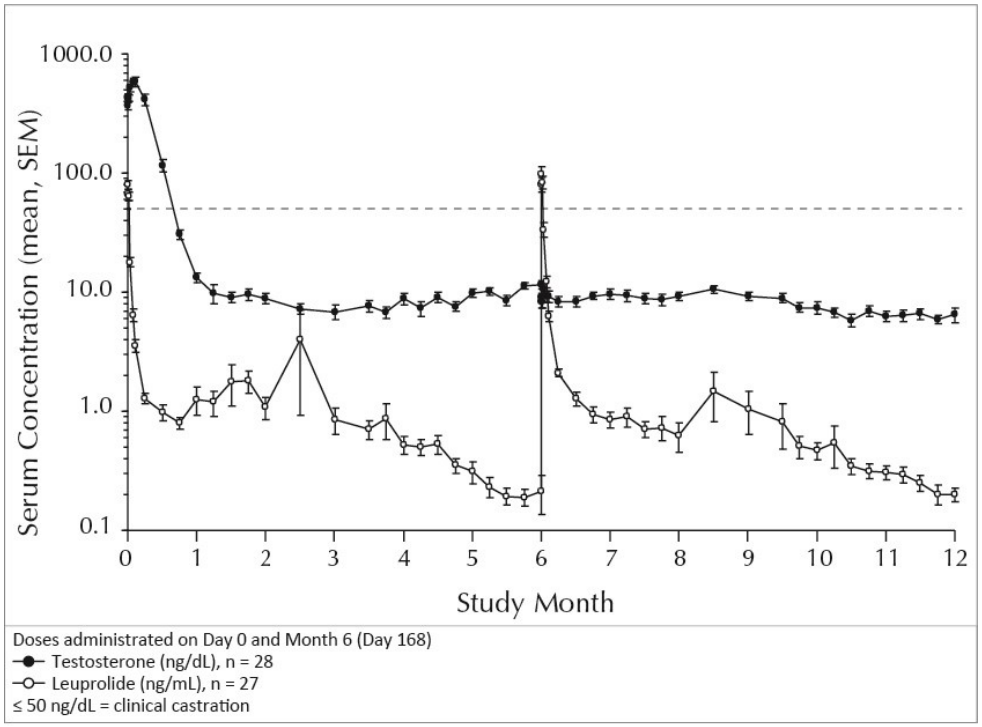
Following subcutaneous administration of ELIGARD across dose levels, serum leuprolide concentrations peaked during the first day then fell rapidly to low, but sustained, concentrations throughout the respective dosing interval (see Section 10.3 Pharmacokinetics). In response to this pattern of leuprolide exposure, serum testosterone levels rose initially then fell to below castrate levels (≤ 50 ng/dL) within 3 weeks after the first dose and were maintained throughout the dosing interval(s) and the planned

duration of each clinical study (see Table 5). The pharmacodynamic response following repeated administration of ELIGARD 45 mg in patients with advanced prostate cancer are shown in Figure 2 and is representative of the PK/PD relationship across all ELIGARD doses. Concentrations of testosterone did not increase upon subsequent injections within each of the clinical studies (see 14 CLINICAL TRIALS for more information regarding response rate for achievement of castrate levels of ≤ 50 ng/dL and ≤ 20 ng/dL).

Table 5. Mean (± SE) Serum Concentrations of Testosterone Following Dosing with ELIGARD

ELIGARD Dose (mg)	Baseline	Day 2/3	Day 21	Remainder of Study [Range]
7.5 (N=20)	408 ± 60 ng/dL	600 ± 74 ng/dL	38 ± 9 ng/dL	7.1 – 17.9 ng/dL
22.5 (N=22)	367 ± 13.2 ng/dL	610 ± 246 ng/dL	28 ± 18 ng/dL	7 – 13 ng/dL
30 (N=24)	385 ± 18.0 ng/dL	588 ± 40 ng/dL	31.7 ± 4.2 ng/dL	6 – 12 ng/dL
45 (N=28)	369 ± 13.3 ng/dL	585 ± 49 ng/dL	30.4 ± 3.0 ng/dL	6 – 12 ng/dL

Figure 2. Serum Concentrations of Leuprolide and Testosterone Following Dosing with ELIGARD 45 mg After Two Subcutaneous Injections at Six-Month Intervals in Patients with Advanced Prostate Cancer.



The initial rise and fall in testosterone levels produced by ELIGARD were of a magnitude and time course 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.

Cardiac Electrophysiology

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

10.2.2 Central Precocious Puberty

In the clinical trial evaluating ELIGARD in pediatric patients with CPP (TOL2581A), there was a transient surge in circulating levels of LH, FSH, estradiol and testosterone following the first administered dose. A decrease in basal and GnRH agonist-stimulated LH and FSH levels along with reductions in basal estradiol and testosterone were observed after repeat administration.

10.3 Pharmacokinetics

Table 6. Summary of Leuprolide Pharmacokinetic Parameters in Patients with Advanced Prostate Cancer Following Administration of ELIGARD

	Initial Release Phase (Administration – Day 3)			Plateau Phase (Day 3-end of interval)			Total Dosing Interval	
	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng hr mL^{-1})	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (ng hr mL^{-1})	C_{last} (ng/mL)	AUC (ng hr mL^{-1})
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

* This single dose study was conducted in bilaterally orchiectomized patients

After an initial subcutaneous injection of ELIGARD 45 mg in pediatric patients 4 to 9 years of age with CPP, leuprolide levels peaked 4 hours postdose with a mean Cmax of 212.3 ng/mL. Absorption occurred in two phases, a burst phase followed by a plateau phase. The mean plateau serum leuprolide level from 4 to 48 weeks was approximately 0.37 ng/mL with a range of 0.18 to 0.63 ng/mL. There was no accumulation of leuprolide after the second dose.

Absorption: The pharmacokinetic parameters of ELIGARD in patients with advanced prostate cancer were determined over one and three dosing intervals for ELIGARD 7.5 mg (1-month) and over two dosing intervals for ELIGARD 22.5 mg (3-month), ELIGARD 30 mg (4-month) and ELIGARD 45 mg (6-month).

After the subcutaneous administration of ELIGARD, an initial release phase characterized by high 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 in males with prostate cancer, however testosterone suppression was maintained. See Table 6 for clinical pharmacokinetic parameters of ELIGARD in patients with prostate cancer. For central precocious puberty, please see above.

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%. The distribution of leuprolide acetate has not been evaluated in pediatric patients.

Metabolism: Leuprolide is a peptide that is primarily metabolized by peptidases and not by CYP enzymes. The major metabolite of leuprolide is a pentapeptide (M-1) metabolite. No metabolism study was conducted with ELIGARD.

Elimination: In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model. No elimination studies have been conducted with ELIGARD.

Special Populations and Conditions:

- **Pediatrics (≥ 2 years of age):** The safety and effectiveness of ELIGARD for the treatment of CPP has been established in pediatric patients 2 years of age and older (see 14 CLINICAL TRIALS).

- **Geriatrics:** The majority (> 70%) of the patients studied in the clinical trials for ELIGARD for prostate cancer were ≥ 70 years of age.

- **Sex:** Only male patients were included in studies with ELIGARD for prostate cancer. Female pediatric patients were included in a clinical study of ELIGARD for the treatment of central precocious puberty.

- **Ethnic Origin:** In the patients studied, mean serum leuprolide concentrations were similar.

- **Hepatic and Renal Insufficiency:** The pharmacokinetic parameters of ELIGARD have not been determined in adult or pediatric patients with hepatic or renal insufficiency.

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

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated between 2°C to 8°C. Once outside the refrigerator this product may be stored in its original packaging at room temperature (15°C to 30 °C) for up to eight weeks prior to mixing and administration.

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

12 SPECIAL HANDLING INSTRUCTIONS

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

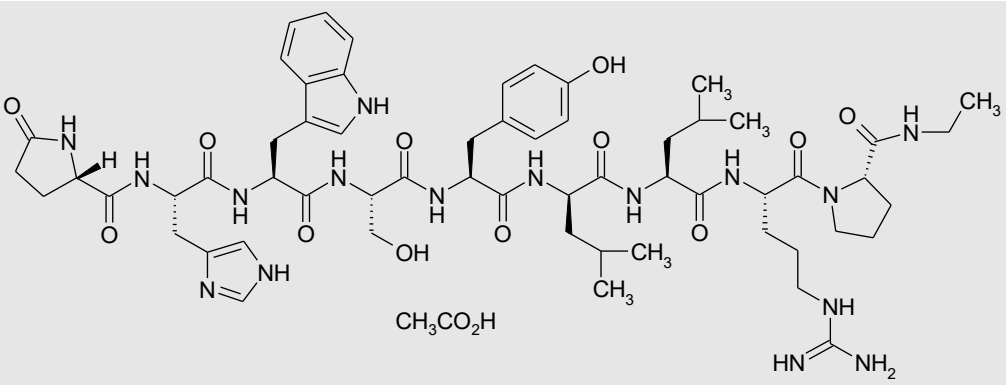
PART II: SCIENTIFIC INFORMATION

13 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:	$C_{59}H_{84}N_{16}O_{12} \bullet C_2H_4O_2$, 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

14.1.1 Prostate Cancer

Open-label, multicentre studies were conducted with each ELIGARD formulation (7.5 mg, 22.5 mg, 30 mg, and 45 mg) in patients with Jewett stage A through D prostate cancer who were treated with at least a single injection of study drug (Table 7 and Table 8). Patients across all four studies with ELIGARD were male with a histologic or cytologic diagnosis of prostatic adenocarcinoma. These studies evaluated the achievement and maintenance of castrate serum testosterone levels over the duration of therapy. The primary endpoint across these studies was the proportion of patients who achieved suppression of serum testosterone to castrate levels (≤ 50 ng/dL) by Month 1. Suppression to castrate

levels was defined as testosterone concentration of ≤ 50 ng/dL for two consecutive timepoints approximately one week apart.

Table 7. Summary of Patient Demographics for Phase 3 Clinical Trials in Patients with Advanced Prostate Cancer

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Jewett Stage
AGL9904	Open-label, uncontrolled, fixed dose, phase 3	ELIGARD 7.5 mg, 6 consecutive subcutaneous doses at monthly intervals Study duration: 6 months	120	72.8 years (52-85)	A: 0% B: 0% C: 74% D: 26%
AGL9909	Open-label, uncontrolled, fixed dose, phase 3	ELIGARD 22.5 mg, 2 consecutive subcutaneous doses at 3-month interval Study duration: 6 months	117	73.1 years (46-85)	A: 2% B: 16% C: 51% D: 31%
AGL0001	Open-label, uncontrolled, fixed dose, phase 3	ELIGARD 30 mg, 2 consecutive subcutaneous doses at 4-month intervals Study duration: 8 months	90	73.5 years (53-84)	A: 2% B: 42% C: 18% D: 38%
AGL0205	Open-label, uncontrolled, fixed dose, phase 3	ELIGARD 45 mg, 2 consecutive subcutaneous doses at 6-month intervals Study duration: 12 months	111	73.2 years (50-86)	A: 4% B: 39% C: 17% D: 40%

Table 8. Results of Phase 3 Clinical Trials in Patients with Advanced Prostate Cancer

Study Number		**AGL9904**	**AGL9909**	**AGL0001**	**AGL0205**
ELIGARD Strength		**7.5 mg**	**22.5 mg**	**30 mg**	**45 mg**
Number of patients with testosterone ≤ 50 ng/dL	Day 28	94% (112/119)	98% (115/117)	96% (85/89)	99% (108/109)
	Day 42	100% (118/118)	99% (116/117)	100% (89/89)	99% (108/109)
	Conclusion	100% (117/117)	100% (111/111)	99% (81/82)	99% (102/103)
Number of patients with testosterone ≤ 20 ng/dL	Day 28	76% (91/119)	84% (98/117)	67% (60/89)	84% (92/109)
	Day 42	97% (115/118)	92% (108/117)	91% (81/89)	95% (104/109)
	Conclusion	98% (115/117)	94% (104/111)	90% (74/82)	87% (90/103)
Mean testosterone concentration (ng/dL)	Baseline	361.3	367.1	385.5	367.7
	Day 28	21.8	15.2	17.2	16.7
	Conclusion	6.1	10.1	12.4	12.6

In the ELIGARD 7.5 mg phase III study (AGL9904), between Day 28 and Day 31, one patient who had achieved castrate suppression was withdrawn. PSA levels were reduced by an average of greater than 90% from baseline during the study.

In the ELIGARD 22.5 mg phase III study (AGL9909), once castrate testosterone suppression was achieved, only one (< 1%) patient demonstrated breakthrough (testosterone levels > 50 ng/dL at anytime during the study after achieving castrate levels). This patient returned to castrate levels following the second injection and remained at castrate levels throughout the study. PSA levels were reduced 98% from baseline to Month 6.

In the ELIGARD 30 mg phase III study (AGL0001), one out of the original 90 patients voluntarily withdrew following the Day 14 visit prior to achieving castrate suppression. Three patients (3.3%) demonstrated testosterone breakthrough (level > 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. Patient PSA levels 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.

In the ELIGARD 45 mg phase III study (AGL0205), 106 of the original 111 patients received two injections. One patient (< 1%) demonstrated testosterone breakthrough (level > 50 ng/dL) during the study. This patient reached castrate suppression at Day 21 and remained suppressed until Day 308 when the testosterone level rose to 112 ng/dL. At Month 12 (Day 336), the testosterone level was 210 ng/dL. All five non-evaluable patients who had achieved castrate testosterone suppression by Day 28 maintained castration at each time point, up to and including the time of withdrawal. Serum PSA decreased in all patients whose baseline concentrations 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 World Health Organization (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.

14.1.2 Central Precocious Puberty

The efficacy of ELIGARD was evaluated in an uncontrolled, open-label, single arm clinical trial in which 64 pediatric patients (62 females and 2 males, naïve to previous GnRH agonist treatment) with CPP received at least one dose of ELIGARD at a dosing interval of 24 weeks and were observed for 12 months. The mean age was 7.5 years (range 4 to 9 years) at the start of treatment. In pediatric patients with CPP, ELIGARD reduced stimulated and basal gonadotropins to prepubertal levels. Suppression of peak stimulated LH concentrations to <4 IU/L was achieved in 87% (95% CI: 76.1%-94.3%) of pediatric patients by month 6 and in 86% of patients by month 12. Suppression of estradiol or testosterone concentration to prepubertal levels at the 6-month assessment was achieved in 97% and 100% of patients, respectively. Suppression of estradiol or testosterone was maintained at the 12-month assessment with 98% (55/56 females) and 50% (1/2 males) maintaining suppression.

ELIGARD arrested or reversed progression of clinical signs of puberty with reductions in growth velocity and bone age. Mean growth velocity decreased from 8.9 ± 13.1 cm/year at 1 month to 6.9 ± 3.1 cm/year at 6 months and to 6.4 ± 1.9 cm/year at 12 months.

Table 9. Summary of Patient Demographics for Phase 3 Clinical Trials in Patients with Central Precocious Puberty

Study #	Study design	Dosage, Route of Administration and Duration	Study Participants (N)	Mean Age / Range (years)	Sex (n)
TOL2581A	Open-label, uncontrolled, fixed dose, phase 3	ELIGARD 45 mg, At least 1 subcutaneous dose at 6-month intervals Study duration: 12 months	64	Mean: 7.5 Range: 4 - 9	2 M, 62 F

Table 10. Reproductive Hormone Levels in Pediatric Patients with CPP Treated with ELIGARD 45 mg Every 6 Months[a]

Endpoint[b]	% (n/N) of Patients Achieving Endpoints			
	Month 3	Month 6	Month 9	Month 12
LH Levels < 4 IU/L	85 (51/60)	87 (54/62)[c]	85 (50/59)	86 (50/58)
Estradiol Levels < 73.4 pmol/L (< 20 pg/mL)	98 (56/57)	97 (58/60)	98 (56/57)	98 (55/56)
Testosterone Levels < 1 nmol/L (< 28.4 ng/dL)	100 (2/2)	100 (2/2)	100 (2/2)	50 (1/2)
FSH Levels < 2.5 IU/L	62 (37/60)	66 (41/62)	44 (26/59)	55(32/58)

[a]Intent-To-Treat Population (N=62)
[b]Post GnRH Agonist Stimulation
[c]Primary Efficacy Endpoint

Eight female patients out of 62 did not meet the primary efficacy criteria for LH < 4 IU/L at 6 months. In four of the eight patients, the LH level at 6 months was between 4.2 and 4.8 IU/L. The remaining four patients had LH levels > 5 IU/L. However, post stimulation estradiol was suppressed to prepubertal levels (< 20 pg/mL) in seven of the eight patients at month 6 and was maintained through month 12.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-Dose Toxicity

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_{50} values greater than 5000 mg/kg (greater than 400 mg/kg of leuprolide acetate) for oral, subcutaneous and intraperitoneal routes of administration, and greater than 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.

Repeat-Dose Toxicity

In a four-month repeat-dose study, rats were treated with ATRIGEL® Delivery System formulations containing 1, 3 or 10 mg/kg leuprolide acetate and ATRIGEL® Delivery System vehicle control (100 µL) subcutaneously twice per month for four months. Lupron Depot® 7.5 mg (10 mg leuprolide acetate/kg) was injected intramuscularly (IM) as a comparative control.

In animals treated with high-dose ELIGARD (10 mg/kg), decreases in organ-to-body weight ratios for the prostate, seminal vesicles, and testes at all termination intervals were noted, consistent with the known pharmacological activity of the drug. Localized injection site lesions such as bruising, excoriation, and scabbing developed in some animals in all treatment groups.

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

Genotoxicity: No mutagenicity, clastogenicity or aneugenicity studies have been conducted specifically with ELIGARD. Leuprolide was not genotoxic in either an in vitro cytogenetics assay using Chinese hamster lung cells, an in vivo micronucleus assay in mice, or the Ames test with five strains of Salmonella typhimurium.

Carcinogenicity: No carcinogenicity studies have been conducted specifically with ELIGARD. 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.

Reproductive and Developmental Toxicology: 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 leuprolide produced reversible atrophy of the testes or accessory sex organs at doses as low as 0.024 mg/kg , and a decrease in LH, FSH and testosterone concentrations. A reversible decrease in copulation and implantation sites was also observed at the high dose of 2.4 mg/kg. No fetal effects were observed.

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

No fetal developmental abnormalities were noted. The sustained release formulation of leuprolide acetate was not teratogenic in rats or rabbits. In the perinatal study, the administration of the sustained release formulation of leuprolide acetate prior to delivery at up to 8 mg/kg demonstrated effects on sex organ weights, but no fetal adverse effects, including sex organ weights.

Special Toxicology: To evaluate the irritation potential of ELIGARD, nonclinical studies were conducted in rats, rabbits, dogs, and pigs across all dosage strengths in both single and repeat dose studies. Histological evaluation of injection sites confirmed foreign body reactions characterized by a mild to moderate irritant response, an effect that is consistent with the subcutaneous administration of an extended-release product. The local irritant effects diminished with time and were generally classified

as a non-irritant 60 days post-dosing compared to a USP negative control. Across nonclinical evaluation of injection site tolerability, erythema and edema were noted in small numbers of animals and were generally considered mild in nature. Dose volume related increases of redness and bruising at the injection site was observed in dogs when large volumes of the formulation were injected (e.g., 0.25 mL – 0.5 mL). The only treatment-related observation was minimal erythema at 6 of 8 injection sites in one animal.

PATIENT MEDICATION INFORMATION FOR PROSTATE CANCER

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrELIGARD®

Leuprolide acetate for extended-release injectable suspension

Powder, 7.5 mg [1-Month], 22.5 mg [3-Month], 30 mg [4-Month], and 45 mg [6-Month], for subcutaneous use

Read this carefully before you start taking **ELIGARD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ELIGARD**.

Serious Warnings and Precautions

ELIGARD may cause the following serious side effects:

- Worsening of the symptoms of prostate cancer at the beginning of the treatment or developing new symptoms such as:
    - bone pain
    - nerve problems such as numbness, tingling, muscle weakness and pain
    - urinary problems such as:
        - blood in your urine
        - difficulty in passing urine
- Bleeding or decreased blood flow to the pituitary gland (pituitary apoplexy). This may occur within the first hour of taking ELIGARD or within 2 weeks of your first dose. Get medical help **right away** if you develop a sudden severe headache, you start vomiting or have changes to your vision and mental health.
- Bone thinning (osteoporosis). ELIGARD may increase your risk of osteoporosis and bone fractures. Your healthcare professional will monitor your risk for bone thinning and bone fractures during treatment with ELIGARD.

What is ELIGARD used for?

ELIGARD (7.5 mg, 22.5 mg, 30 mg, 45 mg) is used in adults for the treatment of advanced prostate cancer.

How does ELIGARD work?

ELIGARD belongs to a group of medicines called luteinizing hormone-releasing hormone (LH-RH) analogs.

When ELIGARD is given regularly to males, it reduces the amount of testosterone produced by the testicles. ELIGARD prevents the growth of prostate cancer cells, which need testosterone to grow. ELIGARD may reduce the symptoms of advanced prostate cancer.

What are the ingredients in ELIGARD?

Medicinal ingredients: Leuprolide acetate

Non-medicinal ingredients: N-methyl-2-pyrrolidone; Poly (DL-lactide-co-glycolide).

ELIGARD comes in the following dosage forms:

Powder for solution: 7.5 mg, 22.5 mg, 30 mg

Powder for suspension: 45 mg

Do not use ELIGARD if:

- you are allergic to:
    - leuprolide acetate or any of the other ingredients in ELIGARD
    - other medicines like ELIGARD (called luteinizing hormone-releasing hormone (LH-RH) analogs)
- you are a female who is 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ELIGARD. Talk about any health conditions or problems you may have, including if you:

- have a history of difficulty passing urine.
- have had a cancer that spread to the spine (backbone) or have a history of spinal cord compression.
- have low red blood cell count (anemia).
- have family history of severe osteoporosis.
- have low bone mineral density.
- are taking any medication that can cause thinning of the bones (such as corticosteroids or anti-seizure medication).
- use alcohol or tobacco.
- have high blood sugar (diabetes). ELIGARD may affect your blood glucose level. Your healthcare professional should monitor you regularly to check your blood glucose levels. If are diabetic you may need to test you blood sugar more frequently while taking ELIGARD.
- are taking medicines used to treat irregular heart rhythm such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone.
- have too low or too high amounts of essential minerals like magnesium, calcium, and potassium (i.e. electrolyte imbalance).
- have heart problems, such as:
    - heart attack
    - have congestive heart failure
    - a heart condition called “Long QT syndrome”
- have had a stroke.
- have a history of brain or spinal cord (central nervous system) problems or tumors.
- have a history of seizures, epilepsy or brain vessel problems.

- are taking medications known to cause seizures like bupropion and selective-serotonin-reuptake inhibitors (SSRIs).

Other warnings you should know about:

- **Hypogonadism:** ELIGARD works by lowering testosterone levels which can trigger hypogonadism. Signs of having low testosterone levels includes loss of sexual desire and impotence. These symptoms may stop at the end of your treatment. Your healthcare professional should monitor you regularly to check your testosterone levels.
- **Interstitial pneumonitis:** Leuprolide-containing products have been associated with inflammation of the lung(s). Tell your healthcare professional right away if you have trouble breathing, shortness of breath at any time, even when you are resting or have a dry cough.
- **Fertility:** Your ability to get pregnant, or father a child, can be lower while taking ELIGARD.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ELIGARD, but are not limited to:

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

How ELIGARD is given:

ELIGARD comes in a pre-connected syringe system whose contents are mixed together by your healthcare professional immediately prior to administration.

- One syringe filled with a powder which is the medicinal ingredient (leuprolide acetate)
- The other syringe is filled with a solution known as the ATRIGEL delivery system

Once mixed, your healthcare professional will inject ELIGARD under the skin (subcutaneously).

The usual dose is:

- one 7.5 mg injection every month
  or
- one 22.5 mg injection every three months
  or
- one 30 mg injection every four months
  or

- one 45 mg injection every six months.

ELIGARD works continuously and consistently over the time between injections.
You and your healthcare professional will decide which treatment plan is right for you. If your situation changes, you and your healthcare professional may need to re-evaluate your treatment plan. Your healthcare professional can help you decide which treatment with ELIGARD is best for you.

Overdose:

If you think you, or a person you are caring for, has been given too much ELIGARD, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Keep all planned visits with your healthcare professional. If you miss an appointment by a few days it should not disrupt the benefits of the treatment. However, getting your injections on time is an important part of the treatment.

What are possible side effects from using ELIGARD?

These are not all the possible side effects you may have when taking ELIGARD. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- Skin rash or bruising
- Feeling tired, weakness
- Fainting
- Nausea, constipation
- Stiff joints or muscles aches and pain
- Waking up during the night to pass urine
- Hair loss
- Feeling sweaty during the night
- Reduced sex drive (libido)
- Trouble sleeping
- Weight gain
- Tenderness in your breasts or enlarged breasts
- Local skin reaction: burning and stinging, pain, redness, itching and/or swelling at the injection site. These reactions may go away after a few days. If the reactions bother you or do not go away, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Feeling lightheaded or dizzy		X	
Hot flushes	X		
Osteoporosis (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking		X	
UNCOMMON			
Blood in your urine or difficulty passing urine		X	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		X	
Difficulty urinating that continues over a long period of time		X	
Feeling nervous		X	
Nausea and vomiting that continues over a long period of time		X	
Numbness in your limbs		X	
Pain in the chest or abdomen		X	
Severe bone pain		X	
Skin ulcer (open wound)		X	
Sweating heavily		X	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		X	
UNKNOWN			
Allergic reactions: sudden wheeziness and chest pain or			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
tightness; or swelling of eyelids, face, lips, tongue or throat			
Convulsions (seizures): uncontrollable shaking with or without loss of consciousness		X	
Interstitial lung disease or pulmonary fibrosis (inflammation of the lung): new onset or worsening of shortness of breath, especially with exertion; dry cough/interstitial lung disease, an inflammation of lung tissue.			X
Pituitary apoplexy (bleeding or decreased blood flow to the pituitary gland): severe headache, vomiting, changes to your vision and mental health.		X	
Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension (increased pressure in your head/around your brain): headache, eye problems, including blurred vision, double vision, decreased eyesight and eye pain, ringing in the ears, dizziness, nausea			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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.

Storage:

Store refrigerated between 2°C to 8°C. Once outside the refrigerator this product may be stored in its original packaging at room temperature (15°C to 30 °C) for up to eight weeks prior to mixing and administration.

Once reconstituted, ELIGARD should be used within 30 minutes. Discard it if it is not used within 30 minutes.

Keep out of reach and sight of children.

If you want more information about ELIGARD:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website [www.tolmar.ca], or by calling 1-844-986-5627.

This leaflet was prepared by Tolmar International Ltd.
Last Revised: January 24, 2024

PATIENT MEDICATION INFORMATION FOR CENTRAL PRECOCIOUS PUBERTY

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrELIGARD®

Leuprolide acetate for extended-release injectable suspension

Powder, 45 mg [6-Month], for subcutaneous use

Read this carefully before you start taking **ELIGARD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ELIGARD**.

What is ELIGARD used for?
ELIGARD (45 mg) is used to treat children 2 years of age and older with central precocious puberty (CPP).

How does ELIGARD work?
ELIGARD prevents the brain from releasing gonadotropin releasing hormone (GnRH). This helps stop the progression of puberty. When it's time for normal puberty to start, your healthcare professional can stop treatment with ELIGARD.

What are the ingredients in ELIGARD?
Medicinal ingredients: Leuprolide acetate
Non-medicinal ingredients: N-methyl-2-pyrrolidone; Poly (DL-lactide-co-glycolide).

ELIGARD comes in the following dosage forms:

Powder for suspension: 45 mg

Do not use ELIGARD if:

- your child is allergic to:
    - leuprolide acetate or to any of the other ingredients in ELIGARD
    - other drugs like ELIGARD (called luteinizing hormone-releasing hormone (LH-RH) analogs). This includes severe allergic reactions (including anaphylactic shock).
- You are female who is pregnant or may become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ELIGARD. Talk about any health conditions or problems your child may have, including if your child:

- have family history of severe osteoporosis.
- have low bone mineral density.
- are taking any medication that can cause thinning of the bones (such as corticosteroids or anti-seizure medication).
- use alcohol or tobacco.
- has a history of mental (psychiatric) problems.
- has a history of brain or spinal cord (central nervous system) problems or tumors.
- have a history of seizures, epilepsy or brain vessel problems.

- are taking medications known to cause seizures like bupropion and selective-serotonin-reuptake inhibitors (SSRIs).

Other warnings you should know about:

- **Slowing down of puberty:** ELIGARD can cause puberty to pause or slow down. Puberty will restart once you stop taking ELIGARD.
- **Puberty symptoms:** ELIGARD may cause an increase in puberty symptoms, like vaginal bleeding. Tell your healthcare professional if these symptoms continue after the second month of taking ELIGARD.
- **Hypogonadism:** ELIGARD works by lowering sex hormone levels which can trigger hypogonadism. Hypogonadism or gonad deficiency occurs when the sex glands produce little or no sex hormones. Sex glands or gonads are ovaries in girls and testes in boys. Your healthcare professional should regularly monitor sex hormone levels.

Pregnancy, Breastfeeding and Fertility (male and female):

- Do not use ELIGARD if you are a female who is or may become pregnant.
    - ELIGARD may cause miscarriage or may cause harm to an unborn baby.
    - Your healthcare professional will do a pregnancy test before you start taking ELIGARD. This test must show that you are not pregnant.
    - Use a non-hormonal birth control method during treatment with ELIGARD.
    - If you get pregnant during treatment, stop taking ELIGARD and talk to your healthcare professional.
- ELIGARD is not recommended for use in breast-feeding females.
- Your ability to get pregnant, or father a child, can be lower while taking ELIGARD.

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will monitor your health.

Your healthcare professional may need to change your child's treatment plan depending on how your child reacts to ELIGARD.

Tell your healthcare professional about all the medicine your child takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ELIGARD, but are not limited to:

- antiarrhythmic medicines (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antipsychotic medicines (used to treat mental disorders) such as: chlorpromazine
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- antifungals (used to treat fungal infections)
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- medicines belonging to a class called beta-2 agonists (used to treat asthma) such as salbutamol
- medicines belonging to a class called 5-HT3 antagonists (used to relieve nausea and vomiting) such as ondansetron

How ELIGARD is given:

ELIGARD comes in a pre-connected syringe system whose contents are mixed together by your healthcare professional immediately prior to administration.

- One syringe filled with a powder which is the medicinal ingredient (leuprolide acetate)
- The other syringe is filled with a solution known as the ATRIGEL delivery system

Once mixed, your healthcare professional will inject ELIGARD under the skin (subcutaneously).

The usual dose is:

- one 45 mg injection every six months.

ELIGARD works continuously and consistently over the time between injections.

Overdose:

If you think you, or a person you are caring for, have taken too much ELIGARD, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Keep all planned visits with your healthcare professional. If you miss an appointment by a few days it should not disrupt the benefits of the treatment. However, getting your injections on time is an important part of the treatment. If a planned dose is missed, your child may start having signs of puberty again.

What are possible side effects from using ELIGARD?

These are not all the possible side effects you may have when taking ELIGARD. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- cold symptoms: nasal congestion, runny nose, sore throat
- wet cough, cough, sudden shortness of breath or wheezing
- stuffy nose, nasal drip, facial pressure, ear and teeth pain or pressure
- abdominal pain, nausea, vomiting, constipation, fever
- headache
- sudden strong feelings of heat and sweating
- weight loss or gain
- lower appetite
- feeling tired, weakness
- stiff joints, muscles aches, spasms or pain
- trouble sleeping

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Abnormal thoughts and behaviour: crying, irritability, restlessness, anger, more aggressive behaviour than normal		X	
Hot flushes	X		
Osteoporosis (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking		X	
Skin reactions, including injection site reactions: burning and stinging, pain, redness, rash, itching and/or swelling, skin sensitive to sunlight	X		
UNCOMMON			
Abnormal swelling of limbs		X	
Severe bone pain		X	
Severe pain in chest		X	
UNKNOWN			
Allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, rash			X
Convulsions (seizures): uncontrollable shaking with or without loss of consciousness		X	
Depression (sad mood that won't goaway): difficulty sleeping or sleepingtoo much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse			
Diabetes: with symptoms such as excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections		X	
Pseudotumor cerebri (PTC) / idiopathic intracranial hypertension (a condition characterized by increased blood pressure in your head/brain): headache, eye problems, including blurred vision, double vision and decreased eyesight, eye pain, ringing in the ears, dizziness, nausea			X
Puberty, increase in hormones (beyond 2 months of receiving ELIGARD): vaginal bleeding, breast enlargement		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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Storage:

Store refrigerated between 2°C to 8°C. Once outside the refrigerator this product may be stored in its original packaging at room temperature (15°C to 30 °C) for up to eight weeks prior to mixing and administration.

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This leaflet was prepared by Tolmar International Ltd.

Last Revised: January 24, 2024

INSTRUCTIONS FOR USE

PrELIGARD®

Leuprolide acetate for extended-release injectable suspension

Powder, 7.5 mg [1-month], 22.5 mg [3-month], 30 mg [4-month] and 45 mg [6-month], for subcutaneous use

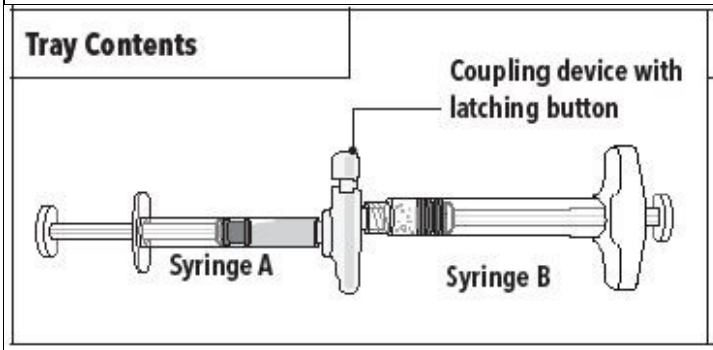
Follow the detailed instructions below to ensure correct preparation of ELIGARD prior to administration:

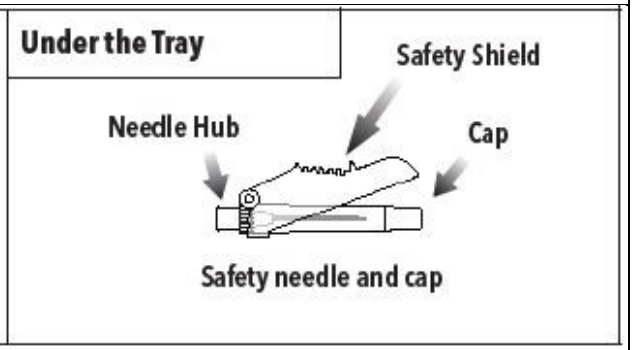
IMPORTANT:

- Use aseptic technique throughout the procedure.
- Gloves are recommended during mixing and administration.
- Allow the product to reach room temperature before mixing by removing it from the refrigerator at least 30 minutes before mixing.
- The product must be administered via subcutaneous injection only.
- Once mixed, the product must be administered within 30 minutes or it should be discarded.

Step 1

On a clean field, open the tray by tearing off the foil from the corner and remove the contents. Discard the desiccant pack. Remove the pre-connected syringe system from the tray. Open the sterile safety needle package by peeling back the paper tab. **Note:** Syringe A and Syringe B should not be lined-up yet. The product should only be administered with the co-packaged, sterile safety needle.

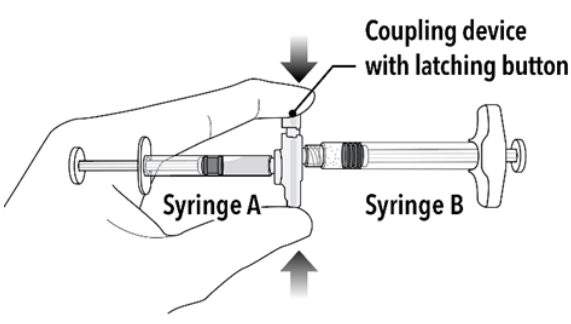


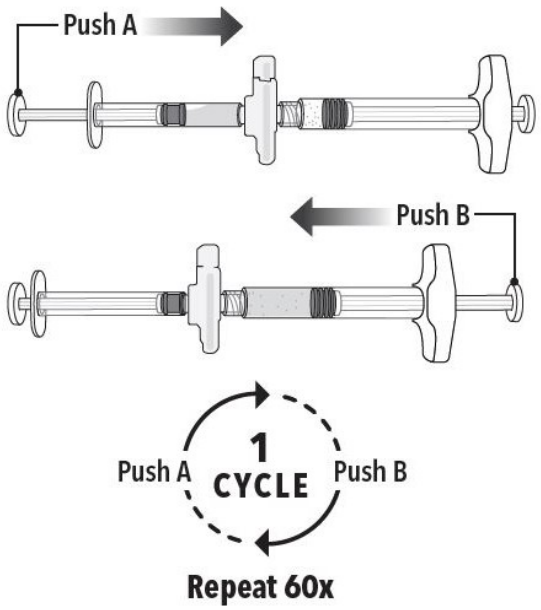
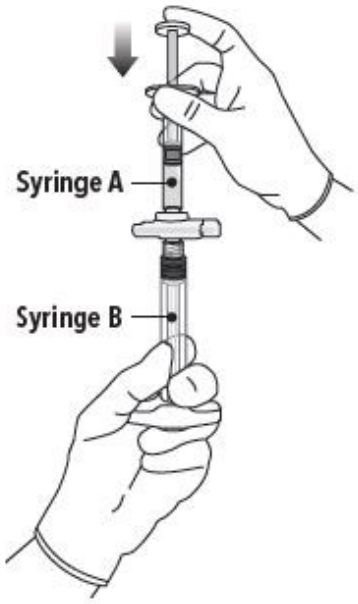


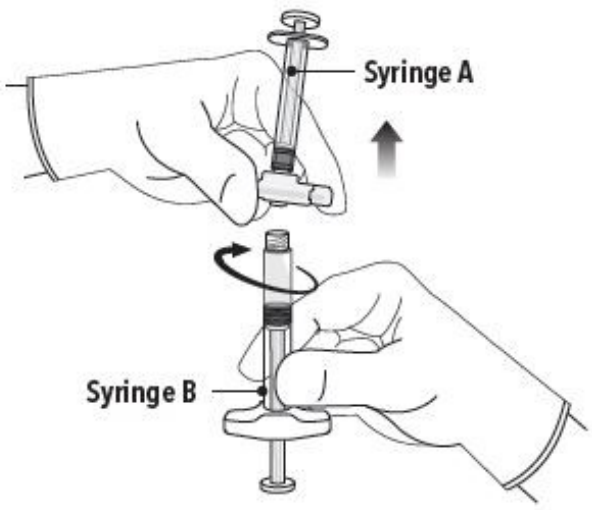
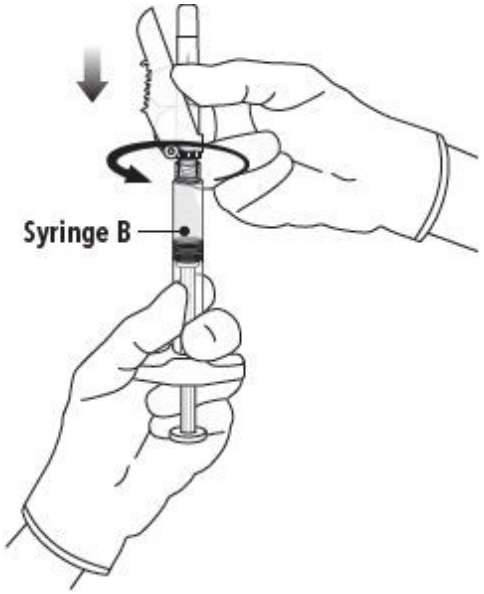
Step 2

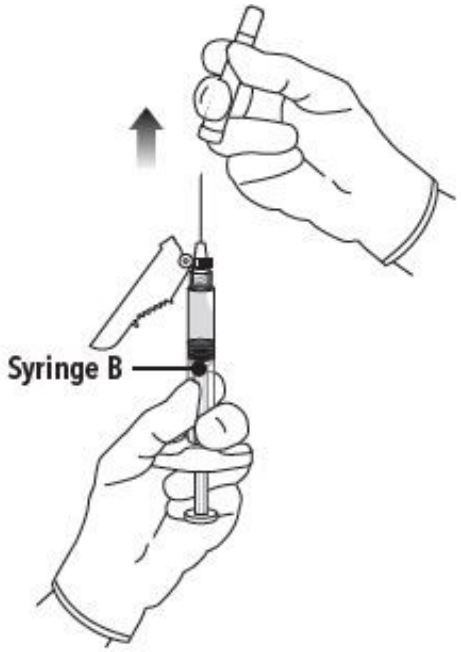
Grasp the latching button on the coupling device with your finger and thumb and press until you hear a snapping sound. The two syringes will be aligned.

Do not bend the pre-connected syringe system.



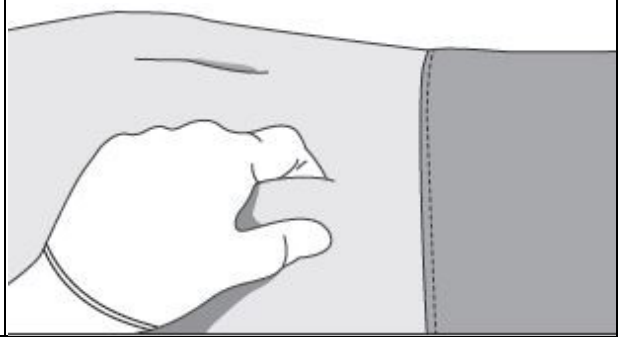
Step 3 Holding the syringes in a horizontal position, **initially** transfer the liquid contents of Syringe A into the leuprolide acetate powder contained in Syringe B. **Thoroughly mix the product for 60 cycles by pushing the contents back and forth between both syringes to obtain a homogenous, viscous suspension.** • **A full cycle is one push of the Syringe A plunger and one push of the Syringe B plunger.** • When thoroughly mixed, the viscous suspension will appear light tan to tan (ELIGARD 7.5 mg) or colorless to pale yellow (ELIGARD 22.5 mg, 30 mg, and 45 mg). **Note:** Product must be mixed as described; shaking will NOT provide adequate mixing. Do not bend.	
Step 4 After mixing, hold the syringes vertically (upright) with Syringe B (wide syringe) on the bottom. The syringes should remain securely coupled. Transfer all of the mixed product into Syringe B by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger.	

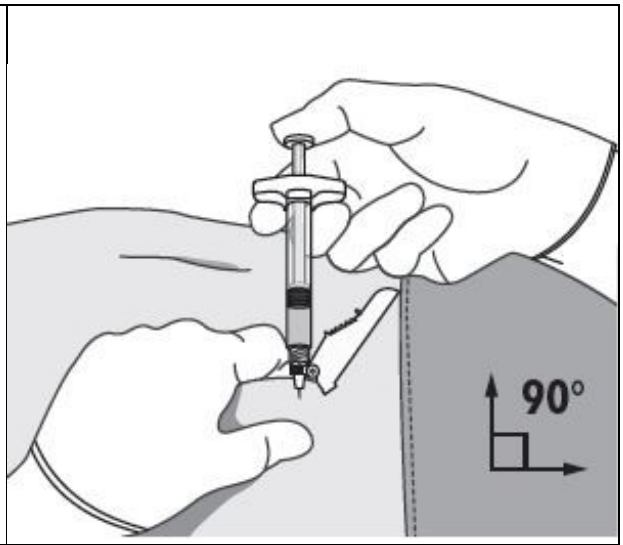
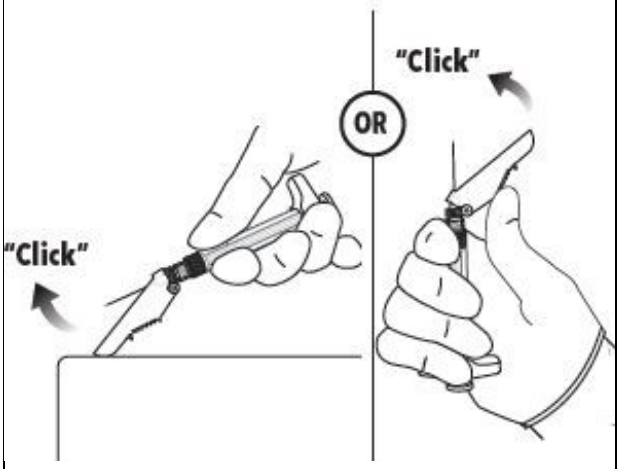
Step 5 While ensuring the Syringe A plunger is fully pushed down, hold the coupling device and unscrew Syringe B. This will disconnect Syringe B from the coupling device. Syringe A will remain attached to the coupling device. **Note:** Small air bubbles will remain in the formulation – this is acceptable. **Do not purge the air bubbles from Syringe B as product may be lost.**	
Step 6 Continue to hold Syringe B upright with the open end at the top. Hold back the white plunger on Syringe B to prevent loss of the product and attach the safety needle and cap. Gently screw clockwise with approximately a three-quarter turn until the safety needle and cap are secure. **Do not overtighten, as the needle hub may become damaged which could result in leakage of the product during injection.** The safety shield may also be damaged if the safety needle and cap are screwed with too much force.	

Step 7 Move the safety shield away from the needle and towards the syringe. Pull off the cap immediately prior to administration.	

Note: Should the needle hub appear to be damaged, or leak, the product should NOT be used. The damaged safety needle and cap should NOT be replaced and the product should NOT be injected. In the event of damage to the needle hub, use a new replacement ELIGARD carton.

Follow the detailed instructions below to ensure correct administration of ELIGARD:

1. Select an injection site on the abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair and hasn't recently been used. 2. Cleanse the injection-site area with an alcohol swab (not enclosed). 3. Using the thumb and forefinger, grab and bunch the area of skin around the injection site.	

4. Using your dominant hand, insert the needle quickly at a 90° angle to the skin surface. The depth of penetration will depend on the amount and fullness of the subcutaneous tissue and the length of the needle. After the needle is inserted, release the skin. 5. Inject the drug using a slow, steady push and press down on the plunger until the syringe is empty. **Make sure all the drug has been injected before removing the needle.** 6. Withdraw the needle quickly at the same 90° angle used for insertion.	
7. Immediately following the withdrawal of the needle, activate the safety shield using a finger/thumb or flat surface and push until it completely covers the needle tip and locks into place. 8. An audible and tactile “click” verifies a locked position. 9. Check to confirm the safety shield is fully engaged. Discard all components safely in an appropriate biohazard container.	

This leaflet was prepared by Tolmar International Ltd.

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