ELIGARD 22.5 MG
ELIGARD 45 MG

1. NAME OF THE MEDICINAL PRODUCT

ELIGARD 22.5 mg powder and solvent for solution for injection
ELIGARD 45 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

		ELIGARD 22.5 mg	**ELIGARD 45 mg**
ATRIGEL Delivery System Syringe	Polymer	PLG	PLG
	Polymer description	Copolymer with hexanediol	Copolymer with hexanediol
	Polymer DL-lactide to Glycolide Molar Ratio	75:25	85:15
Constituted Product	Polymer delivered	158.6 mg	165 mg
	NMP (Liquid carrier) delivered	193.9 mg	165 mg
	Leuprolide acetate delivered	22.5 mg	45 mg
	Leuprolide free base equivalent	20.87 mg	41.7 mg
	Approximate administered formulation weight	375 mg	375 mg
	Approximate injection volume	0.375 mL	0.375 mL

For *a full list of* excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection,

Power (Syringe B):
Pre-filled syringe with a white to off-white powder.

Solvent (Syringe A):
ELIGARD 22.5mg & 45mg: Pre-filled syringe with a clear, colourless to pale yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELIGARD is indicated for the palliative treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

4.2 Posology and method of administration

Dosage for Adult Males

ELIGARD should be administered under the direction of a healthcare professional having the appropriate expertise for monitoring the response to treatment.

ELIGARD 22.5 mg is administered as a single subcutaneous injection every three months. The injected solution forms a solid medicinal product delivery depot and provides continuous release of leuprorelin acetate over a three-month period.

ELIGARD 45 mg is administered as a single subcutaneous injection every six months. The injected solution forms a solid medicinal product delivery depot and provides continuous release of leuprorelin acetate over a six-month period.

As a rule, therapy of advanced prostate cancer with ELIGARD entails long-term treatment and therapy should not be discontinued when remission or improvement occurs.

ELIGARD may be used as neoadjuvant or adjuvant therapy in combination with radiotherapy in high-risk localised and locally advanced prostate cancer.

Response to ELIGARD should be monitored by clinical parameters and by measuring prostate specific antigen (PSA) serum levels. Clinical studies have shown that testosterone levels increased during the first 3 days of treatment in the majority of non-orchiectomised patients and then decreased to below medical castration levels within 3 - 4 weeks. Once attained, castrate levels were maintained as long as medicinal product therapy continued (<1% testosterone breakthroughs). In case the patients's response appears to be sub-optimal it should be confirmed that serum testosterone levels have reached or are remaining at castrate levels.

Administration

The contents of the two pre-filled sterile syringes must be mixed immediately prior to administration of ELIGARD by subcutaneous injection.

Regarding the mixing procedure, see section 6.6.

Based on data from animal experience, intra-arterial or intravenous injection, respectively, has to be strictly avoided.

As with other medicinal products administered by subcutaneous injection, the injection site should be varied periodically.

Paediatric population

Safety and efficacy in children under the age of 18 years have not been established (see also section 4.3).

Dose Adjustment in Specific Patient Populations

No clinical studies were performed in patients with either liver or kidney impairment.

4.3 Contraindications

Hypersensitivity to leuprorelin acetate, to other GnRH agonists or to any of the excipients.

In patients who previously underwent orchiectomy (as with other GnRH agonists, ELIGARD does not result in further decrease of serum testosterone in case of surgical castration).

As sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastases (see also section 4.4)

ELIGARD is contraindicated in women and in paediatric patients.

4.4 Special warnings and special precautions for use

Correct reconstitution: Lack of clinical efficacy may occur due to incorrect reconstitution of the product.
See section 4.2 and section 6.6 for the instructions for preparation and administration of the product and for evaluation of testosterone levels in cases of suspected or known handling errors.

Castration-resistant prostate cancer: In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of castration-resistant prostate cancer. Reference should be made to relevant guidelines.

Androgen deprivation therapy may prolong the QT interval:
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might
prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating ELIGARD.

Cardiovascular diseases: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving GnRH agonists should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Transient testosterone flare: Leuprorelin acetate, like other GnRH agonists, causes a transient increase in serum concentrations of testosterone, dihydrotestosterone and acid phosphatase during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, haematuria, or ureteral or bladder outlet obstruction (see section 4.8). These symptoms usually subside on continuation of therapy.

Additional administration of an appropriate antiandrogen should be considered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone.

Following surgical castration, ELIGARD does not lead to a further decrease in serum testosterone levels in male patients.

Bone density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist (see section 4.8).

Antiandrogen therapy significantly increases the risk for fractures owing to osteoporosis. Only limited data is available on this issue. Fractures owing to osteoporosis were observed in 5% of patients following 22 months of pharmacological androgen deprivation therapy and in 4% of patients following 5 to 10 years of treatment. The risk for fractures owing to osteoporosis is generally higher than the risk for pathological fractures.

Apart from long lasting testosterone deficiency, increased age, smoking and consumption of alcoholic beverages, obesity and insufficient exercise may have an influence on the development of osteoporosis.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of GnRH-agonists, with a majority occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy was presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention is required.

Metabolic Syndrome: The use of GnRH agonists may lead to metabolic changes such as hyperglycemia, diabetes mellitus, and hyperlipidemia. Non-alcoholic fatty liver disease, including cirrhosis, occurred in the postmarketing setting*. Hyperglycemia may represent new-onset diabetes mellitus or worsening of glycemic control in patients with pre-existing diabetes. Monitor for changes in serum lipids, blood glucose and/or glycosylated hemoglobin (HbA1c) in patients receiving a GnRH agonist, and manage according to current treatment guidelines.

Convulsions: Post marketing reports of convulsions have been observed in patients on leuprorelin acetate with or without a history of predisposing factors. Convulsions are to be managed according to the current clinical practice.

Severe Cutaneous Adverse Reactions (SCARs): Severe cutaneous adverse reactions (SCARs), including Steve-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and erythema multiforme occurred in patients receiving Leuprolide Acetate Injectable Formulation.

Monitor patients for the development of SCARs. Advice patients of the signs and symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

If a SCAR is suspected, interrupt leuprolide acetate injectable formulation until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other grade 4 skin reactions, permanently discontinue Leuprolide Acetate Injectable Formulation.

Other events: Cases of ureteral obstruction and spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with GnRH agonists. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Patients with vertebral and/or brain metastases as well as patients with urinary tract obstruction should be closely monitored during the first few weeks of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic drug-drug interaction studies have been performed with ELIGARD. There have been no reports of any interactions of leuprorelin acetate with other medicinal products.

4.6 Pregnancy and lactation

Not applicable as ELIGARD is contraindicated in women.

4.7 Effects on ability to drive and use machines

No studies on the effects of ELIGARD on the ability to drive and use machines have been performed. The ability to drive and operate machines may be impaired due to fatigue, dizziness and visual disturbances being possible side effects of treatment or resulting from the underlying disease.

4.8 Undesirable effects

Adverse reactions seen with ELIGARD are mainly subject to the specific pharmacological action of leuprorelin, namely increases and decreases in certain hormone levels. The most commonly reported adverse reactions are hot flashes, malaise, nausea and fatigue and transient local irritation at the site of injection. Mild or moderate hot flashes occur in approximately 58% of patients.

The following adverse events were reported during clinical trials with ELIGARD in patients with advanced prostatic carcinoma. Adverse events are classified, by frequency, as very common (≥1/10), common (≥100, ,1/10), uncommon (≥1,000, <1/100), rare (≥10,000, <1/1,000), and very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1: ***Undesirable effects in clinical studies with Eligard***

Infections and infestations common uncommon	 nasopharyngitis urinary tract infection, local skin infection
Metabolism and nutrition disorders uncommon	 aggravated diabetes mellitus
Psychiatric disorders uncommon	 abnormal dreams, depression, decreased libido
Nervous system disorders uncommon rare	 dizziness, headache, hypoaesthesia, insomnia, taste disturbance, smell disturbance, vertigo abnormal involuntary movements
Vascular disorders very common uncommon rare	 hot flashes hypertension, hypotension syncope, collapse
Respiratory, thoracic and mediastinal disorders uncommon not known	 rhinorrhoea, dyspnoea interstitial lung disease
Gastrointestinal disorders common uncommon rare	 nausea, diarrhea, gastroenteritis/colitis constipation, dry mouth, dyspepsia, vomiting flatulence, erustation
Skin and subcutaneous tissue disorders very common common uncommon rare unknown	 ecchymoses, erythema pruritus, night sweats clamminess, increased sweating alopecia, skin eruption Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Toxic Skin Eruption, Erythema Multiforme
Musculoskeletal, connective tissues and bone disorders common uncommon	 arthralgia, limb pain, myalgia, rigors, weakness back pain, muscle cramps
Renal and urinary disorders common uncommon	 urinary infrequency, difficulty in micturation, dysuria, nocturia, oliguria bladder spasm, haematuria, aggravated urinary frequency, urinary retention
Reproductive system and breast disorders common uncommon rare	 breast tenderness, testicular atrophy, testicular pain infertility, breast hypertrophy, erectile dysfunction, reduced penis size gynaecomastia, impotence, testicular disorder breast pain
General disorders and administration site reactions very common common uncommon rare very rare	 fatigue, injection site burning, injection site paraesthesia Malaise, injection site pain, injection site bruising, injection site stinging injection site pruritus, lethargy, pain, pyrexia injection site ulceration injection site necrosis
Blood and lymphatic system disorders common	 hematology changes, anaemia
Investigations common uncommon	 increased blood creatinine phosphokinase, prolonged coagulation time increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time, increased weight

Other adverse events which have been reported in general to occur with leuprorelin acetate treatment include peripheral oedema, pulmonary embolism, palpitations, myalgia, an alteration in the skin sensation, muscle weakness, chills, rash, amnesia and visual disturbances.

Muscular atrophy has been observed with long term use of products in this class.

Infarction of pre-existing pituitary apoplexy has been reported rarely after administration of both short and long acting GnRH agonists.

There have been rare reports of thrombocytopenia and leucopenia. Changes in glucose tolerance have been reported.

Convulsions have been reported after GnRH agonist analogue administration.

Local adverse events reported after injection of ELIGARD are similar to the local adverse events associated with similar subcutaneously injected products.

Generally, these localised adverse events following subcutaneous injection are mild and described as being of brief duration.

Anaphylactic/anaphylactoid reactions have been reported rarely after GnRH agonist analogue administration.

Changes in Bone Density
Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH analogues. It can be anticipated that long periods of treatment with leuprorelin may show increasing signs of osteoporosis. Regarding the increased risk for fractures owing to osteoporosis (see section 4.4).

Exacerbation of signs and symptoms of the disease
Treatment with leuprorelin acetate can cause exacerbations of signs and symptoms of the disease during the first few weeks. If conditions such as vertebral metastases and/or urinary obstruction or haematuria are aggravated, neurological problems, such as weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms may occur.

4.9 Overdose

ELIGARD does not have the potential for abuse, and deliberate overdose is unlikely. There are no reports of abuse or overdose having occurred in clinical practice with leuprorelin acetate, but in the event that excessive exposure becomes a reality, observation and symptomatic supportive treatment are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropin releasing hormone analogues
ATC code: L02A E02

ELIGARD®
(leuprolide acetate) for injectable suspension
22.5 mg, 45 mg

Leuprorelin acetate is a synthetic nonapeptide agonist of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis in males. This effect is reversible upon discontinuation of medicinal product therapy. However, the agonist possesses greater potency than the natural hormone and the time to recovery of testosterone levels may vary between patients.

Administration of leuprorelin acetate results in an initial increase in circulating levels of luteinising hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids, testosterone and dihydrotestosterone in males. Continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL).

ELIGARD 22.5 mg : These decreases occur within three to five weeks after initiation of treatment. Mean testosterone levels at six months are 10.1 (± 0.7) ng/dL, comparable to levels following bilateral orchiectomy. All patients who received the full dose of 22.5 mg leuprorelin in the pivotal clinical study reached castrate levels at 5 weeks; 99 % had reached this by day 28. In the vast majority of patients the testosterone levels seen were below 20 ng/dL although the full benefit of these low levels has not yet been established. PSA levels decreased by 98% over six months.

ELIGARD 45 mg: These decreases occur within three to four weeks after initiation of treatment. Mean testosterone levels at six months are 10.4 (± 0.53) ng/dL, comparable to levels following bilateral orchiectomy. All but one patient who received the full dose of 45 mg leuprorelin in the pivotal clinical study reached castrate levels at 4 weeks In the vast majority of patients the testosterone levels seen were below 20 ng/dL although the full benefit of these low levels has not yet been established. PSA levels decreased by 97% over six months.

Long-term studies have shown that continuation of therapy maintains testosterone below the castrate level for up to seven years, and presumably indefinitely.

Tumour size was not measured directly during the clinical trial programme, but there was an indirect beneficial tumour response as shown by a 98% reduction in mean PSA for ELIGARD 22.5mg and 97% reduction for ELIGARD 45 mg.

In a phase III randomized clinical trial including 970 patients with locally advanced prostate cancer (mainly T2c-T4 with some T1c to T2b patients with pathological regional nodal disease) of whom 483 were assigned to short-term androgen suppression (6 months) in combination with radiation therapy and 487 to long-term therapy (3 years), a non-inferiority analysis compared the short-term to long-term concomitant and adjuvent hormonal treatment with GnRH agonist (triptorelin or goserelin). The 5-year overall mortality was 19.0% and 15.2%, in the short-term and long-term groups, respectively. The observed Hazard Ratio of 1.42 with an upper one-sided 95.71% CI of 1.79 or two-sided 95.71% CI of 1.09; 1.85 (p = 0.65 for non inferiority), demonstrate that the combination of radiotherapy plus 6 months of androgen deprivation therapy provides inferior survival as compared with radiotherapy plus 3 years of androgen deprivation therapy. Overall survival at 5 years of long-term treatment and short-term treatment shows 84.8% survival and 81.0%, respectively. Overall quality of life using QLQ-C30 did not differ significantly between the two groups (P=0.37). Results are dominated by the population of patients with locally advanced tumours.

Evidence for the indication of high-risk localized prostate cancer is based on published studies of radiotherapy combined with GnRH analogues, including leuprorelin acetate. Clinical data from five published studies were analyzed (EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 8610, and D'Amico et al., JAMA, 2004), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy. Clear differentiation of the respective study populations for the indications locally advanced prostate cancer and high-risk localized prostate cancer was not possible in the published studies.

Clinical data have shown that radiotherapy followed by 3 years of androgen deprivation therapy is preferable to radiotherapy followed by 6 months of androgen deprivation therapy. The recommended duration of androgen deprivation therapy in medical guidelines for T3-T4 patients receiving radiotherapy is 2-3 years.

5.2 Pharmacokinetic properties

Absorption:
ELIGARD 22.5 mg:
In patients with advanced carcinoma of the prostate, mean serum leuprorelin concentrations following the initial injection rise to 127 ng/ml at 4.6 hr (Cmax) after injection. After the initial increase following each injection (the plateau phase from 3 - 84 days after each dose), serum concentrations remained relatively constant (0.2 - 2 ng/ml). There is no evidence of accumulation during repeated dosing.

ELIGARD 45 mg:
In patients with advanced carcinoma of the prostate, mean serum leuprorelin concentrations following the initial injection rise to 82 ng/ml at 4.4 hr (Cmax) after injection. After the initial increase following each injection (the plateau phase from 3 - 168 days after each dose), serum concentrations remained relatively constant (0.2 - 2 ng/ml). There is no evidence of accumulation during repeated dosing.

Distribution: The mean steady-state volume of distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27 litres. In vitro binding to human plasma proteins ranged from 43% to 49%.

Elimination: In healthy male volunteers, a 1 mg bolus of leuprorelin acetate 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 excretion studies have been conducted with ELIGARD.

No drug metabolism study was conducted with ELIGARD.

5.3 Preclinical safety data

Preclinical studies with leuprorelin acetate, revealed in both sexes effects on the reproductive system, which were expected from the known pharmacological properties. These effects were shown to be reversible after discontinuation of the treatment and an appropriate period of regeneration. Leuprorelin acetate did not show teratogenicity. Embryotoxicity/lethality was observed in rabbits, in line with the pharmacological effects of leuprorelin acetate on the reproductive system.

Carcinogenicity studies were performed in rats and mice over 24 months. In rats, a dose-related increase in pituitary apoplexy was observed after subcutaneous administration at doses of 0.6 to 4 mg/kg/day. No such effect was observed in mice.

Leuprorelin acetate and related one-month product ELIGARD 7.5 mg were not mutagenic in a set of in vitro and in vivo assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ELIGARD 22.5 mg
Solvent (syringe A): Poly (DL-lactic-co-glycolic-acid) (75:25)
N-Methylpyrrolidone

ELIGARD 45 mg
Solvent (syringe A): Poly (DL-lactic-co-glycolic-acid) (85:15)
N-Methylpyrrolidone

Power (syringe B): None

6.2 Incompatibilities

The leuprorelin present in syringe B must only be mixed with the solvent in syringe A and must not be mixed with other medicinal products.

6.3 Shelf life

2 years

After first opening of the tray, the powder and solvent for solution for injection are to be immediately reconstituted and administered to the patient.

Once reconstituted: use immediately, as the viscosity of the solution increases with time.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C); in the original package in order to protect from moisture. This product must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use. Once outside the refrigerator this product may be stored in its original packaging at room temperature (below 25°C) for up to eight weeks. Keep out of children. Jauhi daripada kanak-kanak.

6.5 Nature and contents of container

A pre-connected syringe system consisting of:
- one pre-filled cyclic olefin copolymer syringe containing powder (Syringe B)
- one pre-filled polypropylene syringe containing solvent (Syringe A)
- a connector with latching button for Syringe A and B.

Syringe A has a plunger tip of thermoplastic rubber. The plunger tip of Syringe B is composed of chlorobutyl rubber.

The following pack sizes are available:
ELIGARD 22.5mg:
- A kit consisting of a thermoformed tray and a 20-gauge sterile needle in a cardboard carton. The tray contains one pre-connected syringe system and a desiccant pouch.
- A bundle pack containing kits of 3 pre-connected syringe system

ELIGARD 45 mg:
- A kit consisting of a thermoformed tray and a 18-gauge sterile needle in a cardboard carton. The tray contains one pre-connected syringe(s) system and a desiccant pouch.
- A bundle pack containing kits of 2 pre-connected syringe system

MANUFACTURED BY:
Tolmar Inc.
1201 Cornerstone Drive,
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USA

Revision date: June 2026

04006676 Rev. 2 06/26

6.6 Special precautions for disposal and other handling

Allow the product to come to room temperature by removing from the refrigerator approximately 30 minutes prior to use.
Please prepare the patient for injection first, followed by the preparation of the product, using the instructions below. If the product is not prepared using the proper technique, it should not be administered, as lack of clinical efficacy may occur due to incorrect reconstitution of the product.

Step 1:
On a clean field, open the tray by tearing off the foil from the corners to remove the contents. Discard the desiccant pouch. Remove the pre-connected syringe system (Figure 1.1) from the tray. Open the safety needle package (Figure 1.2) by peeling back the paper tab. Note: Syringe A and Syringe B should not be lined-up yet.

Figure 1.1
Tray Contents: pre-connected syringe system

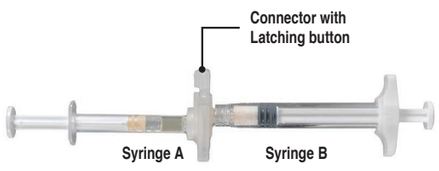
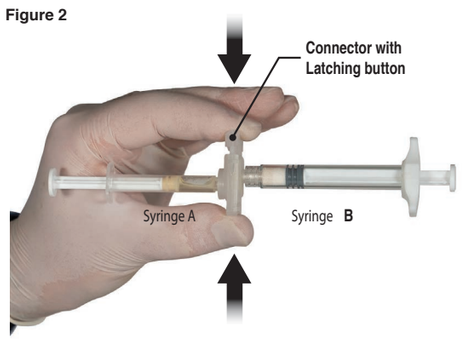


Figure 1.1
Under the Tray: safety needle and cap



Step 2:
Grasp the latching button on the connector with your finger and thumb and press (Figure 2) until you hear a snapping sound. The two syringes will be lined up. No particular orientation of the syringe system is required to activate the connector. Do not bend the syringe system (please note that this may cause leakage as you may partially unscrew the syringes).

Figure 2



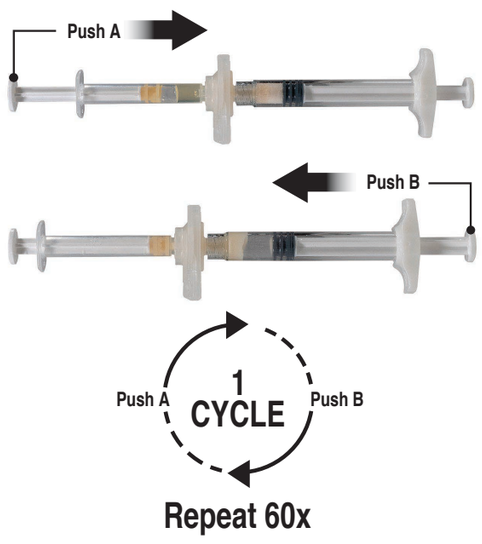
Step 3:
Holding the syringes in a horizontal position, transfer the liquid contents of Syringe A into the leuprorelin acetate powder contained in Syringe B. Thoroughly mix the product for 60 cycles by gently pushing the contents of both syringes back and forth between both syringes (a cycle is one push of the plunger for Syringe A and one push of the plunger for Syringe B) in a horizontal position to obtain a homogenous, viscous solution (Figure 3). Do not bend the syringe system (please note that this may cause leakage as you may partially unscrew the syringes).

Figure 3

When thoroughly mixed, the viscous solution will appear with a colour in the range of colourless to white to pale brown (which could include shades of white to pale yellow).

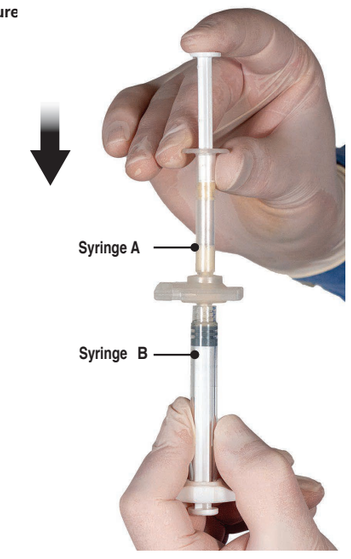
Important: After mixing proceed with the next step immediately as the product gets more viscous over time. Do not refrigerate the mixed product.

Please note: Product must be mixed as described; shaking WILL NOT provide adequate mixing of the product.



Step 4:
After mixing, hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (short, wide syringe) by pushing down the Syringe A plunger and slightly withdrawing the Syringe B plunger (Figure 4).

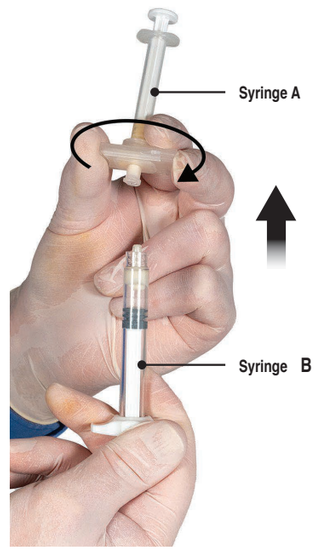
Figure



Step 5:
While ensuring Syringe A plunger is fully pushed down, hold the connector and unscrew it from Syringe B. Syringe A will remain attached to the connector (Figure 5). Ensure that no product leaks out as the needle will then not secure properly when attached.

Please note: one large or a few small air bubbles may remain in the formulation - this is acceptable. **Please do not purge the air bubbles from Syringe B at this stage as product may be lost!**

Figure 5



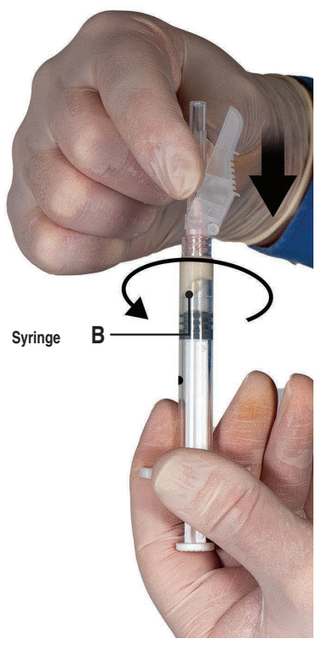
Step 6:
- Hold Syringe B upright and hold back the white plunger to prevent loss of the product.
- Secure the safety needle to Syringe B by holding the syringe and gently turning the needle clockwise with approximately a three-quarter turn until the needle is secure (Figure 6).

Do not over tighten as this may cause cracking of the needle hub resulting in leakage of the product during injection. The safety shield may also be damaged if the needle is screwed with too much force.

Should the needle hub crack, appear to be damaged, or have any leakage, the product should not be used. The damaged needle should not be substituted/replaced and the product should not be injected. The entire product should be disposed of securely

In the event of damage to the needle hub, a new replacement product should be used.

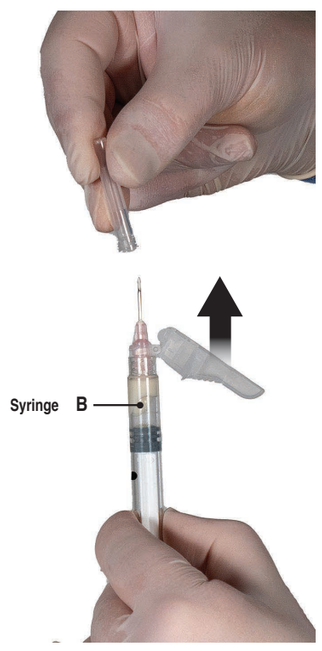
Figure 6



Step 7:
Move the safety shield away from the needle and pull off the protective needle cover immediately prior to administration (Figure 7).

Important: Do not operate the safety needle mechanism before administration. Should the needle hub appear to be damaged, or leak, the product should NOT be used. The damaged needle should NOT be replaced and the product should NOT be injected. In the event of damage to the needle hub, use another ELIGARD kit.

Figure 7



Step 8:
Prior to administration, purge any large air bubbles from Syringe B. Administer the product subcutaneously whilst keeping the safety shield away from the needle.

Administration Procedure:
- 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 has not recently been used.
- Cleanse the injection-site area with an alcohol swab (not enclosed).
- Using the thumb and forefinger, grab and bunch the area of skin around the injection site.
- 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.
- Inject the drug using a slow, steady push and press down on the plunger until the syringe is empty. Please ensure that the full amount of the product in Syringe B is injected before removing the needle.
- Withdraw the needle quickly at the same 90° angle used for insertion while maintaining pressure on the plunger.

Figure 8



Step 9:
After injection, lock the safety shield using any of the activation methods listed below.

1. Closure on a flat surface
Press the safety shield, lever side down, onto a flat surface (Figure 9a) to cover the needle and lock the shield.

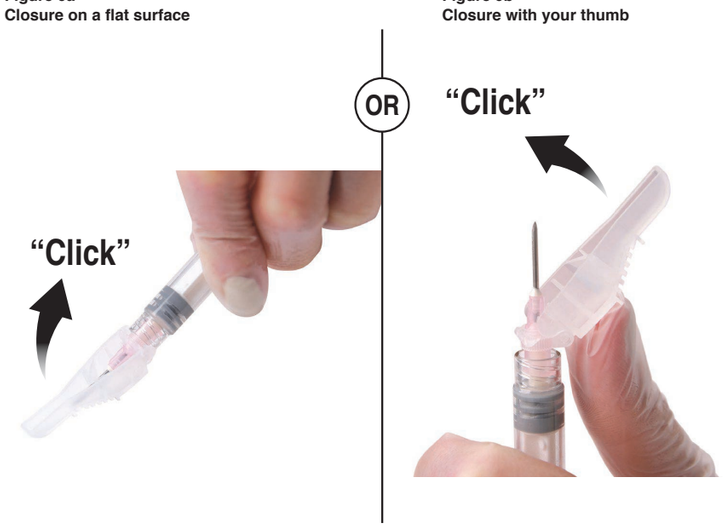
Verify locked position through audible and tactile “click”. Locked position will completely cover needle tip.

2. Closure with your thumb
Placing your thumb on the safety shield (Figure 9b), cover the needle tip and lock the shield.

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

Figure 9a
Closure on a flat surface

Figure 9b
Closure with your thumb



Once safety shield is locked, immediately dispose of the needle and syringe in an approved sharps container.