Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ELIGARD 22.5 mg powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prefilled syringe with powder for solution for injection contains 22.5 mg leuprorelin acetate, equivalent to 20.87 mg leuprorelin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection**.**

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

Solvent (Syringe A):
Pre-filled syringe with a clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ELIGARD 22.5 mg is indicated for the 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

Posology
Adult Males

ELIGARD should be administered under the direction of a healthcare professional having available 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.

As a rule, therapy of advanced prostate cancer with ELIGARD 22.5 mg entails long-term treatment and therapy should not be discontinued when remission or improvement occurs.

ELIGARD 22.5 mg may be used as neoadjuvant or adjuvant therapy in combination with radiotherapy in high-risk localised and locally advanced prostate cancer.

Response to ELIGARD 22.5 mg 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 patient's response appears to be sub-optimal, it should be confirmed that serum testosterone levels have reached or are remaining at castrate levels. As lack of efficacy may result from incorrect preparation, reconstitution, or administration, testosterone levels should be evaluated in cases of suspected or known handling errors (see section 4.4).

In patients with metastatic castration resistant prostate cancer not surgically castrated receiving a GnRH agonist, such as leuprorelin, and eligible for treatment with androgen biosynthesis inhibitors or androgen receptor inhibitors, treatment with a GnRH agonist may be continued.

Paediatric population
The safety and efficacy of ELIGARD 22.5 mg in children aged 0 to 18 years have not been established (see also section 4.3).

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

Method of administration
ELIGARD 22.5 mg should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures. Instructions for reconstitution and administration must be strictly followed (see section 4.4 and 6.6.). If the product is not prepared appropriately, it should not be administered.

The contents of the two pre-filled sterile syringes must be mixed immediately prior to administration of ELIGARD 22.5 mg by subcutaneous injection.
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.

4.3 Contraindications

ELIGARD 22.5 mg is contraindicated in women and in paediatric patients.
Hypersensitivity to leuprorelin acetate, to other GnRH agonists or to any of the excipients listed in section 6.1.

In patients who previously underwent orchiectomy (as with other GnRH agonists, ELIGARD 22.5 mg 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)

4.4 Special warnings and precautions for use

Correct reconstitution: Cases of handling errors which can occur during any step of the preparation process, and which could potentially result in lack of efficacy have been reported. Instructions for reconstitution and administration must be strictly followed (see section 6.6). In cases of suspected or known handling error, patients should be monitored appropriately (see section 4.2).

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 22.5 mg.

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 22.5 mg 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 GnRH agonists (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 changes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes. Metabolic changes associated with GnRH agonist may also include fatty liver disease.
Convulsions: Post marketing reports of convulsions have been observed in patients on leuprorelin acetate therapy with or without a history of predisposing factors. Convulsions are to be managed according to the current clinical practice.
Idiopathic intracranial hypertension: idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving leuprorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of leuprorelin should be considered.
Severe cutaneous adverse reactions: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) which can be life-threatening or fatal, have been reported in association with leuprorelin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these reactions appear, leuprorelin should be withdrawn immediately and an alternative treatment considered (as appropriate).

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 22.5 mg. There have been no reports of any interactions of leuprorelin acetate with other medicinal products.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ELIGARD 22.5 mg with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Not applicable as ELIGARD 22.5 mg is contraindicated in women.

4.7 Effects on ability to drive and use machines

No studies on the effects of ELIGARD 22.5 mg 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 22.5mg are mainly subject to the specific pharmacological action of leuprorelin acetate, namely increases and decreases in certain hormone levels. The most commonly reported adverse reactions are hot flashes, nausea, malaise and fatigue and transient local irritation at the site of injection. Mild or moderate hot flashes occur in approximately 58% of patients.

Tabulated list of adverse reactions

The following adverse events were reported during clinical trials with ELIGARD 22.5 mg in patients with advanced prostate carcinoma. Adverse events are classified, by frequency, as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <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	nasopharyngitis
uncommon	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	dizziness, headache, hypoaesthesia, insomnia, taste disturbance, smell disturbance, vertigo
rare	abnormal involuntary movements
not known	idiopathic intracranialhypertension (pseudotumor cerebri) (see section 4.4)
Cardiac disorders not known	QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	
very common	hot flashes
uncommon	hypertension, hypotension
rare	syncope, collapse
Respiratory, thoracic and mediastinal disorders	
uncommon	rhinorrhoea, dyspnoea
not known	interstitial lung disease
Gastrointestinal disorders	
common	nausea, diarrhoea, gastroenteritis/colitis
uncommon	constipation, dry mouth, dyspepsia,vomiting
rare	flatulence, eructation,
Skin and subcutaneous tissue disorders	
very common	ecchymoses, erythema
common	pruritus, night sweats
uncommon	clamminess, increased sweating
rare	alopecia, skin eruption
unknown	Stevens-Johnsonsyndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic SkinEruption, Erythema Multiforme
Musculoskeletal and connective tissues disorders	
common	arthralgia, limb pain, myalgia, rigors, weakness
uncommon	back pain, muscle cramps
Renal and urinary disorders	

common	urinary infrequency, difficulty in micturation, dysuria, nocturia, oliguria
uncommon	bladder spasm, haematuria, aggravated urinary frequency, urinary retention
Reproductive system and breast disorders	
common	breast tenderness, testicular atrophy, testicular pain infertility, breast hypertrophy, erectile dysfunction, reduced penis size
uncommon	gynaecomastia, impotence, testicular disorder
rare	breast pain
General disorders and administration site conditions	
very common	fatigue, injection site burning, injection site paraesthesia
common	malaise, injection site pain, injection site bruising, injection site stinging
uncommon	injection site pruritus, injection site induration, lethargy, pain, pyrexia
rare	injection site ulceration
very rare	injection site necrosis
Blood and lymphatic system disorders	
common	hematology changes, anaemia
Investigations	
common	increased blood creatinine phosphokinase, prolonged coagulation time
uncommon	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, muscle weakness, an alteration in the skin sensation, 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 (see section 4.4).

Local adverse events reported after injection of ELIGARD 22.5 mg 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 analogue. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

ELIGARD 22.5mg 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

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). 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.

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 22.5 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 adjuvant 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: In patients with advanced carcinoma of the prostate, mean serum leuprorelin concentrations following the initial injection rise to 127ng/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.

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 22.5 mg.

No drug metabolism study was conducted with ELIGARD 22.5 mg.

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

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

Powder (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

Once the product has been removed from the refrigerator, it may be stored in the original packaging at room temperature (below 25°C) for up to four weeks.

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 four weeks.

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:

- 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 2 pre-connected syringe system

Not all pack sizes may be marketed.

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

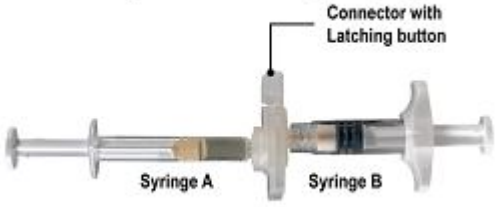
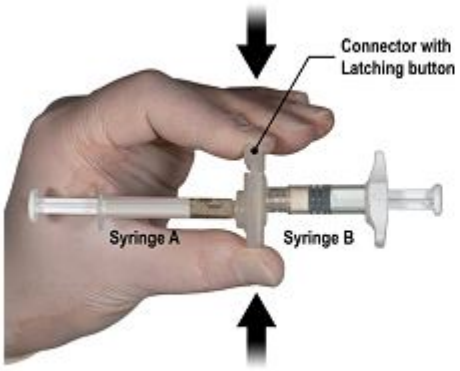


Figure 1.2
Under the Tray: safety needle and cap


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).

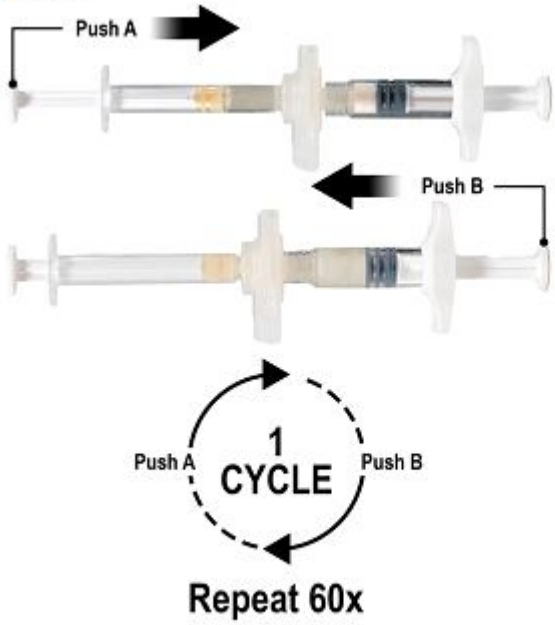
Figure 2



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 yellow (which could include shades of white to pale yellow).

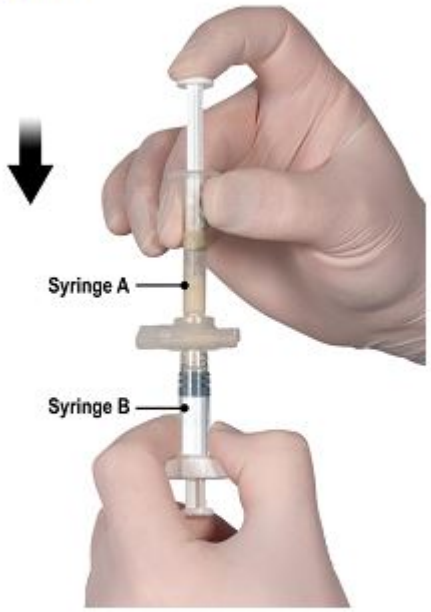
Important: After mixing proceed with the next step immediately as the product gets more viscous over time. Do not refrigerate the mixed product.

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).

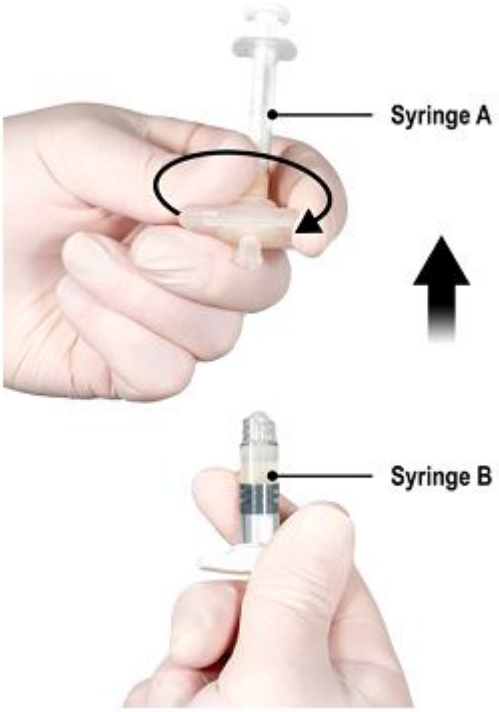
Figure 4



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

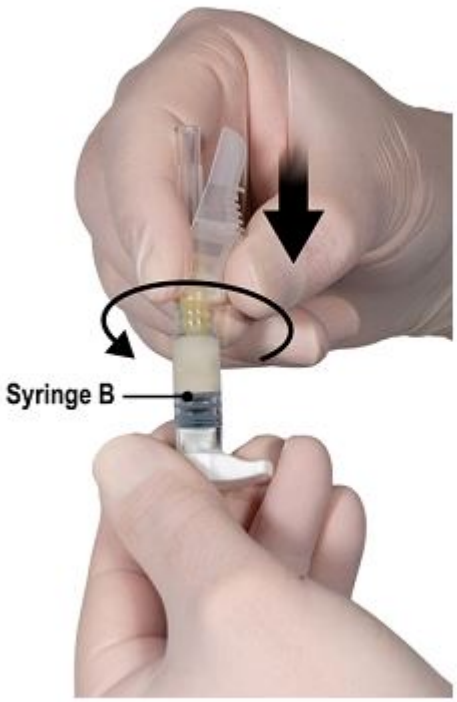
- Hold Syringe B upright and hold back the white plunger to prevent loss of the product.

- 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 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.

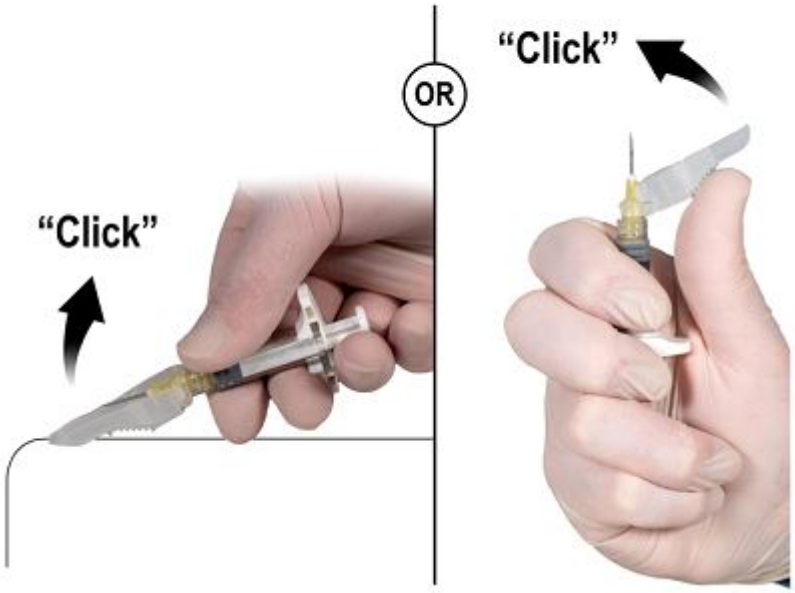
2. Closure with your thumb

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.

7 MARKETING AUTHORISATION HOLDER

Recordati Industria Chimica e Farmaceutica SpA
Via Matteo Civitali
20148
Milan
Italy

8 MARKETING AUTHORISATION NUMBER

PA0812/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 20 December 2009

10 DATE OF REVISION OF THE TEXT

October 2024