SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ELIGARD® 45 mg enjeksiyonluk çözelti için s.c. toz içeren şırınga ve çözücü içeren şırınga
Steril

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each prefilled syringe contains 45 mg leuprorelin acetate, equivalent to 41.7 mg leuprorelin.

Syringe A: Contains 434 mg of sterile solvent for reconstitution of ELIGARD 45 mg.
Syringe B: Contains 59.2 mg leuprorelin acetate
After mixing with 434 mg of solvent, 45 mg/unit is obtained.

Excipients:
For the excipients, see section 6.1.

3. PHARMACEUTICAL FORM

For solution for s.c injection syringe containing powder and syringe containing solvent.

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 is indicated

- For the treatment of hormone dependent advanced prostate cancer
- For the treatment of high-risk prostate limited or spread to the region of the prostate hormone dependent prostate cancer in combination with radiotherapy.

4.2 Posology and method of administration

Posology/ frequency of administration and duration:

Adult Males

ELIGARD is administered as a single subcutaneous injection every 6 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 should be administered under the direction of a healthcare professional having available the appropriate expertise for monitoring the response to treatment.

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 above castration level (50 ng/dl)). 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.

Method of administration:
ELIGARD should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures. *(For instructions on reconstitution of the medicinal product before administration, see section 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 by subcutaneous injection.

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

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

Additional information on special populations:
Kidney / Kidney impairment:
No clinical studies were performed in patients with either liver or kidney impairment. Therefore, no special warning is available.

Paediatric population
The safety and efficacy of ELIGARD in children aged 0 to 18 years have not been established *(See section 4.3).* It is not applicable to children. ELIGARD is contraindicated in pediatric patients *(See Section 4.3).*

Geriatric population:
No special warning is available.

4.3 Contraindications

ELIGARD is contraindicated in the following conditions:

- In case of 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 section 4.4)*
- In women and in paediatric patients.

4.4 Special warnings and 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.

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 45 mg.

Cardiovascular diseases: 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 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.

Hyperglycemia and diabetes: 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.

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.

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.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ELIGARD 45 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)*.

Additional information on special populations:
There are no interaction studies.

Paediatric population
There are no interaction studies

4.6 Pregnancy and lactation

General recommendation
Pregnancy category is: X

Women of childbearing potential/Birth control (Contraception)

Not applicable as ELIGARD is contraindicated in women.

Pregnancy
Not applicable as ELIGARD is contraindicated in women.
ELIGARD is contraindicated during pregnancy.

Risk Summary
Based on findings in animal studies and mechanism of action, ELIGARD may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Expected hormonal changes that occur with ELIGARD treatment increase the risk for pregnancy loss. In animal developmental and reproductive studies, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation in rats. Pregnant patients and women of reproductive potential should be informed of the potential risk to the fetus.

Animal Data
In animal developmental and reproductive studies, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects of fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug.

Lactation
Not applicable as ELIGARD is contraindicated in women.

The safety and efficacy of ELIGARD have not been established in females. There is no information regarding the presence of ELIGARD in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in a breastfed child from ELIGARD, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Reproduction / Fertility:
Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis in men. As a result, reproductive ability is reversibly affected.

Based on mechanism of action, ELIGARD may impair fertility in males of reproductive potential

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. Therefore, patients should be warned to be careful while driving and using machines.

4.8 Undesirable effects

Adverse reactions seen with ELIGARD 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 hot flashes occur in approximately 58% of patients.

The following adverse events were reported during clinical trials with ELIGARD in patients with advanced prostate carcinoma.

The following adverse reactions have been reported by MedDRA system-organ class and frequency with the following approach:

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).

Adverse reactions reported in clinical studies with ELIGARD

Infections and infestations
Common : Nasopharyngitis
Uncommon : Urinary tract infection, local skin infection

Blood and lymphatic system disorders
Common: Hematology changes, (decrease in red blood cell count and hematocrit), anaemia (decrease in hemoglobin)

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

Cardiac disorders
Not known : QT prolongation *(see sections 4.4*)

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

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

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 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 to Turkish Pharmacovigilance Center (TÜFAM) via www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel:0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose and treatment

ELIGARD does not have the potential for abuse, and therefore 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: L02AE02.

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 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 97% reduction in mean PSA for ELIGARD.

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

General characteristics

Absorption:

In patients with advanced carcinoma of the prostate, mean serum leuprorelin concentrations following the initial injection rise to 82ng/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%.

Biotransformation:
No drug metabolism studies have been conducted with ELIGARD.

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 elimination studies have been conducted with ELIGARD.

Linearity/non-linearity
The pharmacokinetic release profile of leuprorelin, the active ingredient of the injected ELIGARD product, is non-linear over time due to the characteristics of a slow-release polymer formulation. Each ELIGARD dosage formulation has a non-linear release characteristic.

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 six-month product ELIGARD 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-glycolite) (85:15)
N-methyl-2- pyrrolidone
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

Unopened packaging: 24 months

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.

The product, which is reconstituted for use with sterile solvent, must be applied immediately due to microbiological aspects and the viscosity of the solution increases with time. It is for single use only.

6.4 Special precautions for storage

Store in a refrigerator (between temperatues 2°C – 8°C) and 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.

Do not freeze. Do not thaw and use frozen products

6.5 Nature and contents of container

There are two pre-filled syringes, one cyclic olefin copolymer syringe containing powder (Syringe B), and one polypropylene syringe containing solvent (Syringe A). Together the two syringes comprise a mixing system.

Syringe A has a plunger tip of thermoplastic rubber and is capped with a polyethylene or polypropylene Luer Lock cover. The syringe tip cap is composed of bromobutyl rubber and the two plunger tips of Syringe B are composed of chlorobutyl rubber.

A kit consisting of two thermoformed trays in a cardboard carton. One tray contains one pre-filled polypropylene syringe A, a large plunger rod and a desiccant pouch. The other tray contains pre-filled cyclic olefin copolymer syringe B, a sterile needle and a silicone desiccant pouch.

6.6 Special precautions for disposal and other handling

Unused product or waste materials should be disposed of according to the regulations on “Control of Medicinal Wastes” and “Control of Packaging and Packaging Wastes”.

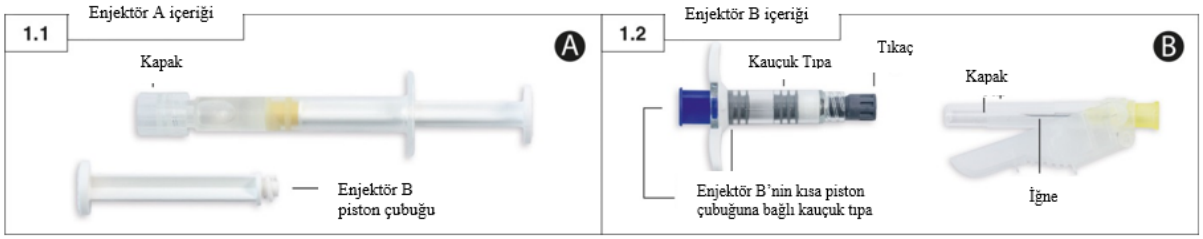
Preparation for use:
Allow the product to come to room temperature by removing from the refrigerator approximately 30 minutes prior to use.

Please prepare the patient for injection first, followed by the preparation of the product, using the instructions below.

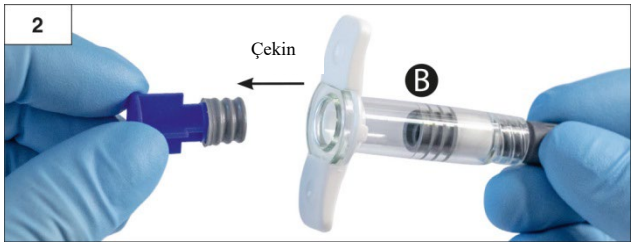
If the product is not prepared using the proper technique, it should not be administered, as lack of clinical efficacy may occur due to incorrect reconstitution of the product.

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

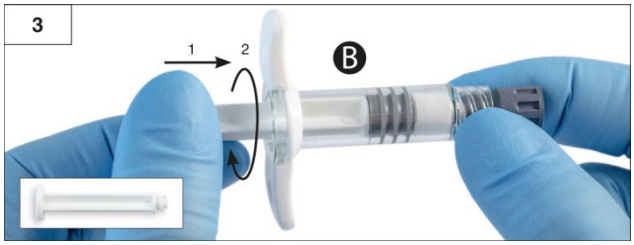
Step 1: Open both trays (tear off the foil from the corner which can be recognized by a small bubble) and empty the contents onto a clean field (two trays containing Syringe A (Figure 1.1) and Syringe B (Figure 1.2)). Discard the desiccant pouches.



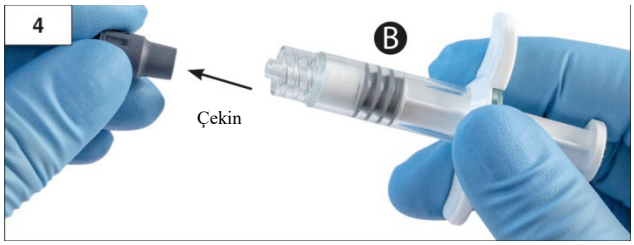
Step 2: **<u>Pull out</u>** and **<u>do not unscrew</u>** the blue coloured short plunger rod together with the attached grey stopper from Syringe B and discard (Figure 2). **Do not attempt to mix the product with two stoppers in place.**



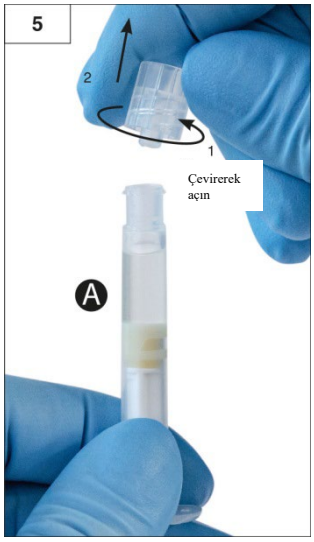
Step 3: Gently screw the Syringe B white plunger rod to the remaining grey stopper in Syringe B (Figure 3).



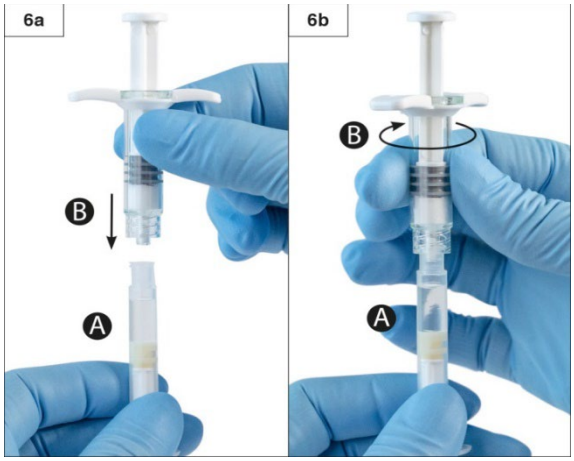
Step 4: Remove the grey rubber cap from Syringe B and put down the Syringe (Figure 4).



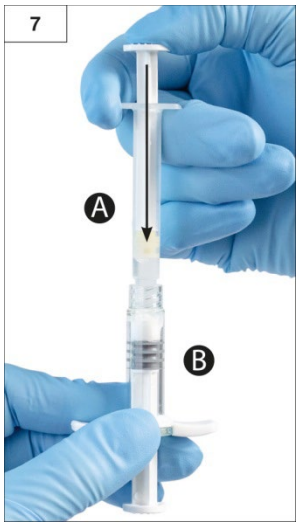
Step 5: Hold Syringe A in a vertical position to ensure no liquid leaks out and unscrew the clear cap from Syringe A (Figure 5).



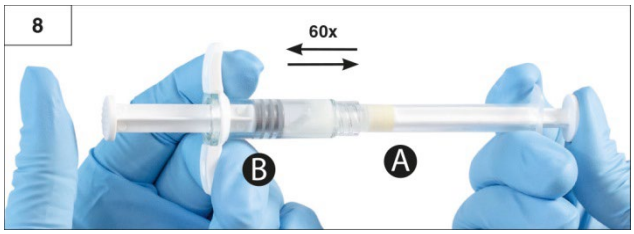
Step 6: Join the two syringes together by pushing in and twisting Syringe B onto Syringe A until secure (Figure 6a and 6b). **Do not over tighten**.



Step 7: Flip the connected unit over and continue to hold the syringes vertically with Syringe B on the bottom while injecting the liquid contents of Syringe A into Syringe B containing the powder (leuproreline acetate) (Figure 7).



Step 8: Thoroughly mix the product by gently pushing the contents of both syringes back and forth between syringes (60 times in total, which takes approximately 60 seconds) in a horizontal position to obtain a homogenous, viscous solution (Figure 8). Do not bend the syringe system (please note that this may cause leakage as you may partially unscrew the syringes).

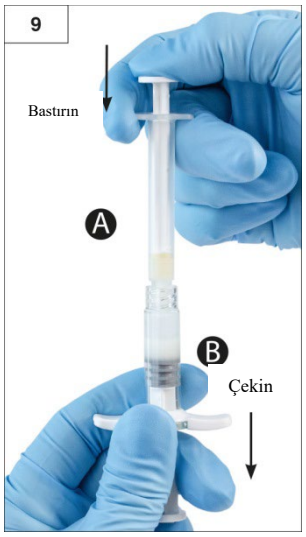


When thoroughly mixed, the viscous solution will appear with a colour in the range of colourless to white to pale yellow (which could include shades of white to pale yellow).

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

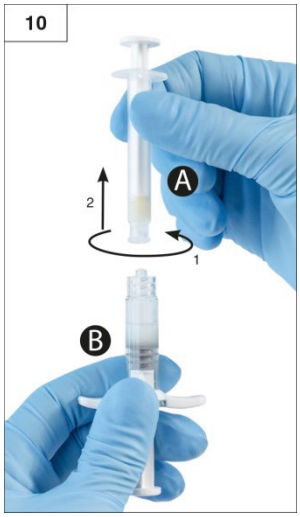
Please note: Product must be mixed as described; shaking WILL NOT provide adequate mixing of the product.

Step 9: Hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (wide syringe) by pushing down the Syringe A plunger and slightly withdrawing the Syringe B plunger (Figure 9).



Step 10: Twist off Syringe A while continuing to push down on the Syringe A plunger (Figure 10). 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!**



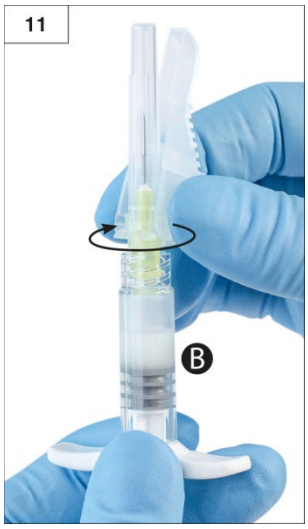
Step 11:

- Hold Syringe B upright and hold back the white plunger to prevent loss of the product.
- Open pack of the safety needle by peeling back paper tab and take out safety needle. Do not remove the hinged safety shield.
- 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 11).

Do not over tighten as this may cause cracking of the needle hub resulting in leakage of the product during injection.

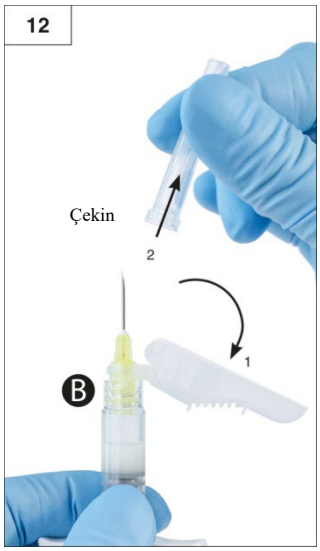
Should the needle hub crack, appear to be damaged, or have any leakage, the product should not be used. The damaged needle should not be substituted/replaced and the product should not be injected. The entire product should be disposed of securely

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



Step 12: Move the safety shield away from the needle and pull off the protective needle cover prior to administration (Figure 12).

Important: Do not operate the safety needle mechanism before administration.

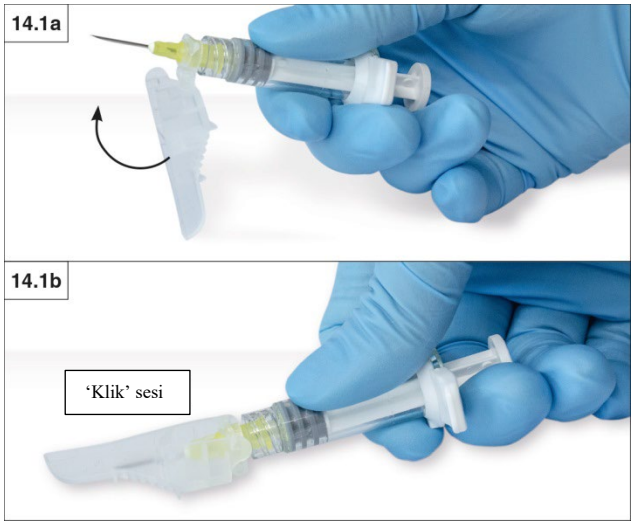


Step 13: Prior to administration, purge any large air bubbles from Syringe B. Administer the product subcutaneously whilst keeping the safety shield away from the needle. Please ensure that the full amount of the product in Syringe B is injected.

Step 14: After injection, lock the safety shield using any of the activation methods listed below.

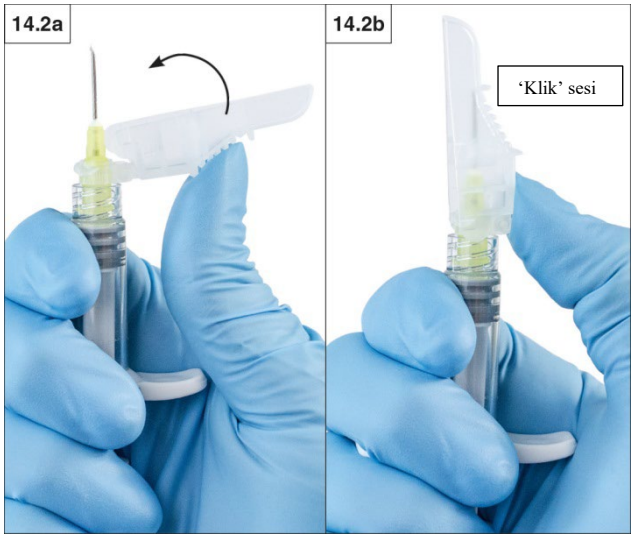
1. Closure on a flat surface
Press the safety shield, lever side down, onto a flat surface (Figure 14.1a and b) to cover the needle and lock the shield.

Verify locked position through audible and tactile “click”. Locked position will completely cover needle tip (figure 14.1b).



2. Closure with your thumb
Placing your thumb on the safety shield (Figure 14.2a), cover the needle tip and lock the shield.

Verify locked position through audible and tactile “click”. Locked position will completely cover needle tip (figure 14.2b).



Step 15: Once safety shield is locked, immediately dispose of the needle and syringe in an approved sharps container.

7. MARKETING AUTHORISATION HOLDER

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