1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ELIGARD ® 7,5 mg

ELIGARD ® 22,5 mg

ELIGARD ® 45 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ELIGARD ® 7,5 mg:

One prefilled syringe with powder for solution for injection contains 7,5 mg leuprorelin acetate, equivalent to 7,0 mg leuprorelin.

ELIGARD ® 22,5 mg:

One prefilled syringe with powder for solution for injection contains 22,5 mg leuprorelin acetate, equivalent to 21,0 mg leuprorelin.

ELIGARD ® 45 mg:

One prefilled syringe with powder for solution for injection contains 45 mg leuprorelin acetate, equivalent to 41,7 mg leuprorelin.

For 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.

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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 palliative treatment of advanced prostate cancer.

4.2 Posology and method of administration

Posology

- ELIGARD is administered subcutaneously and provides continuous release of leuprolide acetate over a one-, three- or six-month treatment period.
- The injection delivers the dose of leuprolide acetate incorporated in a polymer formulation**.**

ELIGARD RECOMMENDED DOSING:

Dose	**7,5 mg**	**22,5 mg**	**45 mg**
Recom-mended dose	1 injection every month	1 injection every 3 months	1 injection every 6 months

Method of administration

- Injection.

Use aseptic technique throughout the procedure. The use of gloves is recommended during mixing and administration. Allow the product to reach room temperature before mixing. Once mixed, the product must be administered within 30 minutes or it should be discarded.

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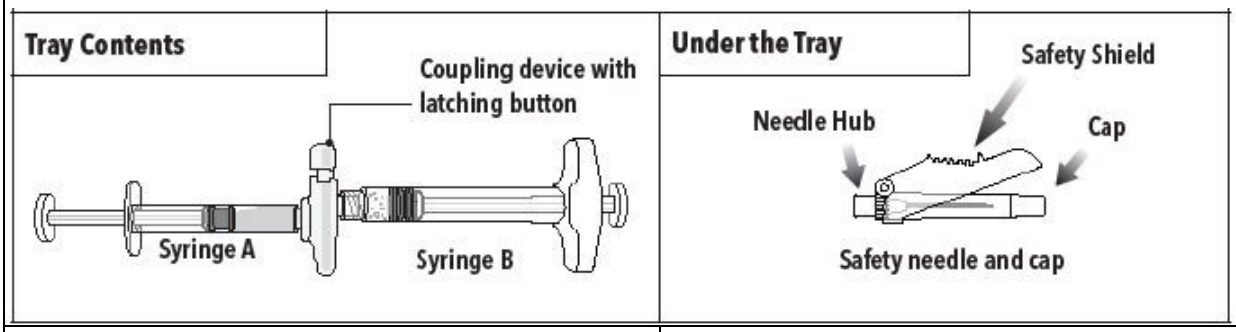
Follow the detailed instructions below to ensure correct preparation of ELIGARD prior to administration:

Step 1

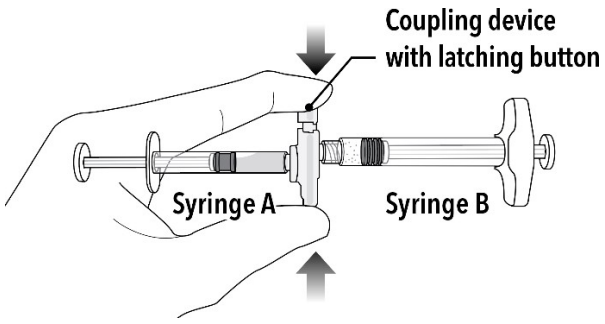
On a clean field open the tray by tearing off the foil from the corner and remove the contents. Discard the desiccant pack. Remove the pre-connected syringe system from the tray. Open the sterile safety needle package by peeling back the paper tab. **Note:** Syringe A and Syringe B should not be lined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

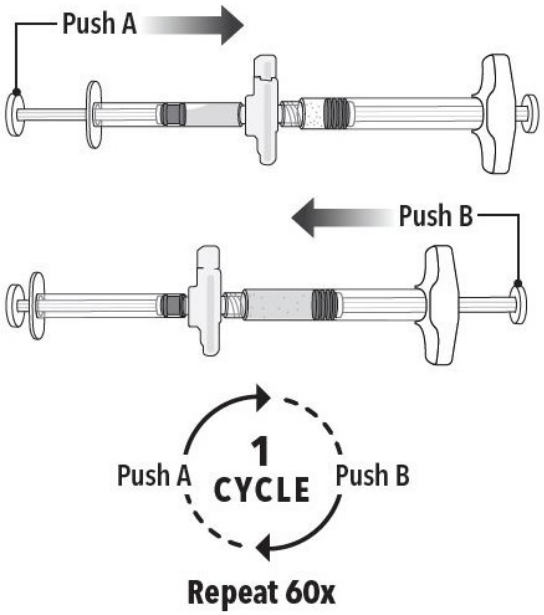


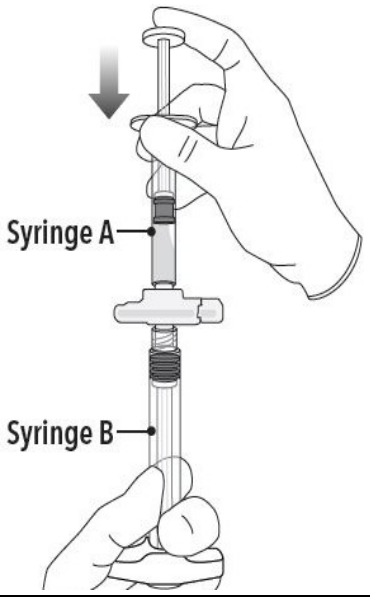
Step 2

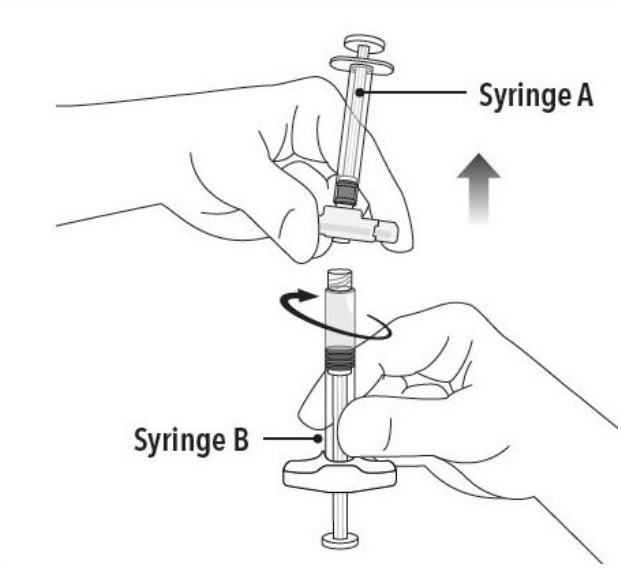
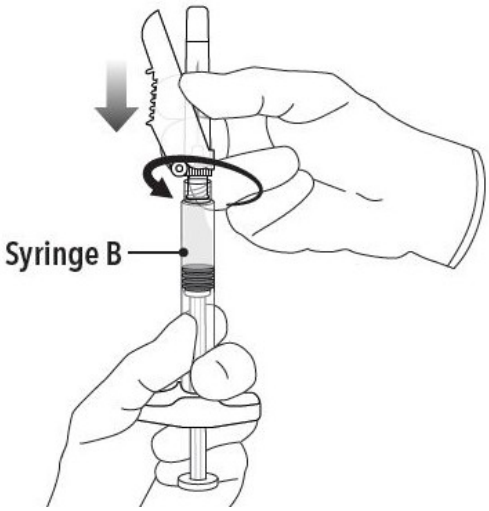
Grasp the latching button on the coupling device with your finger and thumb and press until you hear a snapping sound. The two syringes will be aligned.

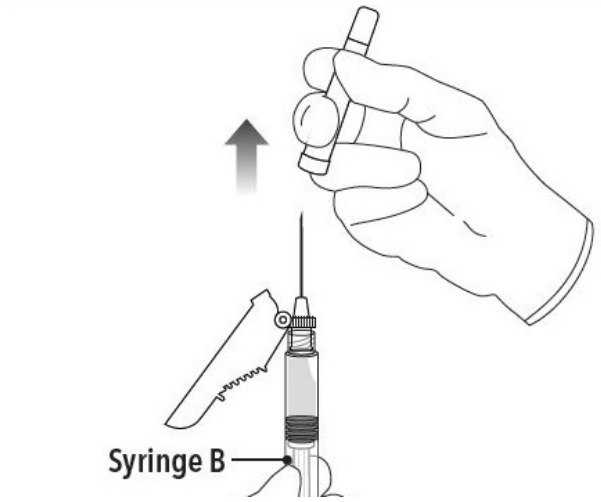
Do not bend the pre-connected syringe system.



Step 3 Holding the syringes in a horizontal position, transfer the liquid contents of Syringe A into the leuprolide acetate powder contained in Syringe B. **Thoroughly mix the product for 60 cycles by pushing the contents back and forth between both syringes to obtain a uniform suspension.** • **A cycle is one push of the Syringe A plunger and one push of the Syringe B plunger.** • When thoroughly mixed, the suspension will appear colorless to pale yellow. **Note:** Product must be mixed as described; shaking will NOT provide adequate mixing. Do not bend.	

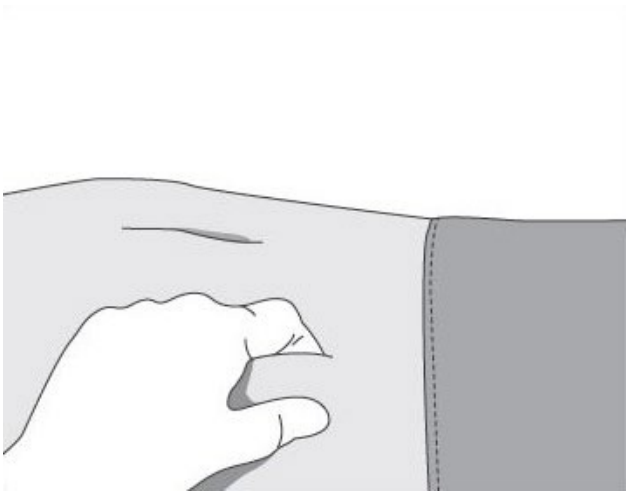
Step 4 After mixing, hold the syringes vertically (upright) with Syringe B (wide syringe) on the bottom. The syringes should remain securely coupled. Transfer all of the mixed product into Syringe B by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger.	

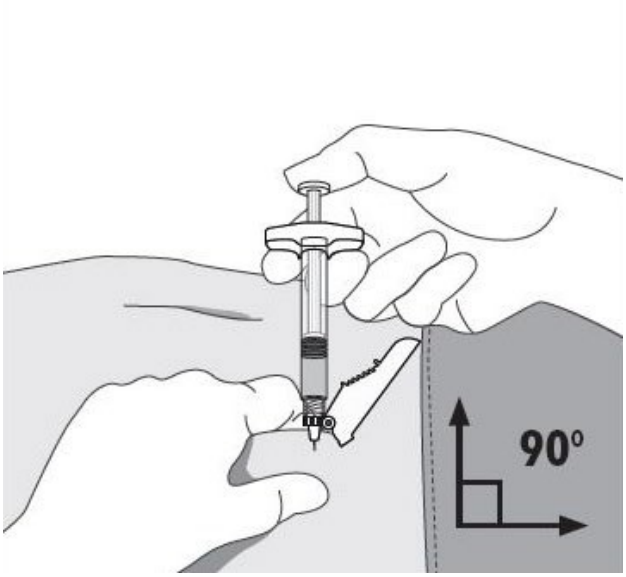
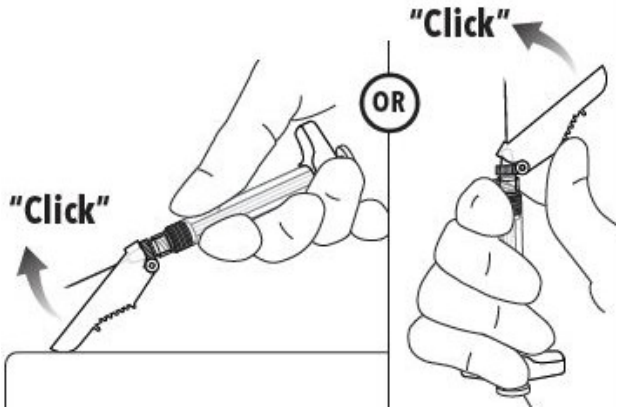
Step 5 While ensuring the Syringe A plunger is fully pushed down, hold the coupling device and unscrew Syringe B. This will disconnect Syringe B from the coupling device. Syringe A will remain attached to the coupling device. **Note:** Small air bubbles will remain in the formulation – this is acceptable.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

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

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

Administration Procedure:

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

4. Using your dominant hand, insert the needle quickly at a 90° angle to the skin surface. The depth of penetration will depend on the amount and fullness of the subcutaneous tissue and the length of the needle. After the needle is inserted, release the skin. 5. Inject the drug using a slow, steady push and press down on the plunger until the syringe is empty. 6. **Make sure all the drug has been injected before removing the needle.** 7. Withdraw the needle quickly at the same 90° angle used for insertion.	
8. Immediately following the withdrawal of the needle, activate the safety shield using a finger/thumb or flat surface and push until it completely covers the needle tip and locks into place. 9. An audible and tactile “click” verifies a locked position. 10. Check to confirm the safety shield is fully engaged. Discard all components safely in an appropriate biohazard container.	

4.3 Contraindications

- ELIGARD is contraindicated in patients with hypersensitivity to leuprorelin acetate, GnRH agonist analogues or any of the excipients of ELIGARD listed in Section 6.1.
- **Anaphylactic reactions to synthetic GnRH or GnRH agonist analogues have been reported in the literature.**
- Pregnancy and lactation (see *Section 4.6*).
- ELIGARD is contraindicated in women and in paediatric patients.

- 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*).

4.4 Special warnings and precautions for use

Transient testosterone flare:

ELIGARD 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 signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, haematuria, or bladder outlet obstruction (*see section 4.8*).

Other events:

ELIGARD causes a transient increase in serum testosterone concentrations during the first one or two weeks of treatment. Therefore, potential exacerbation of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or haematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH agonists, such as ELIGARD. If spinal cord compression or ureteral obstruction develops, standard treatment of these complications should be instituted.

Hyperglycemia and diabetes:

There is increased reporting of risk for hyperglycemia and developing diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists, such as ELIGARD, for prostate cancer; it is important for healthcare professionals to evaluate patients for risk factors for these diseases. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitoring of blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist is needed. Healthcare professionals should always carefully weigh the benefits and risks of using GnRH agonists, such as ELIGARD, before determining appropriate treatment for prostate cancer.

***C*ardiovascular**:

Androgen deprivation therapy may prolong the QT interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking medicines known to prolong the QT interval (*see section 4.5*). Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Doctors should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating ELIGARD.

Laboratory tests:

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

In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were routinely reached within two to four weeks and once achieved was maintained for the duration of treatment.

Respiratory:

There have been post-marketing reports of interstitial pneumonitis associated with leuprorelin use. Treatment should be discontinued immediately if the patient develops any signs or symptoms suggestive of interstitial lung disease.

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 as contained in

ELIGARD should be withdrawn immediately and an alternative treatment considered (as appropriate).

4.5 Interaction with other medicines and other forms of Interaction

- No pharmacokinetic-based interaction studies were conducted with ELIGARD.
- *Medicine/Laboratory test interactions:*

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

ELIGARD is contraindicated in pregnancy *(see section 4.3*).

- ELIGARD is contraindicated in women and in paediatric patients and was not studied in women or children.

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- ELIGARD can cause foetal harm when administered to pregnant women. Major foetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation.
- There was increased foetal mortality and decreased foetal weights in rats and rabbits.
- The effects on foetal mortality are expected consequences of the alterations in hormonal levels brought about by ELIGARD.
- The possibility exists that spontaneous abortion may occur.

Breastfeeding

ELIGARD is contraindicated in lactation (*see section 4.3*).

Fertility

No information available.

4.7 Effects on ability to drive and use machines

ELIGARD may impair mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision, due to fatigue, dizziness and visual disturbances being possible side effects of treatment or resulting from the underlying disease.

4.8 Undesirable effects

Summary of the safety profile

During the clinical trials, injection sites were closely monitored.

Local side effects at the injection site were as follows:

- Burning/ stinging sensation in 34, 6 % of injections for the 7,5 mg strength; 21,7 % of injections for the 22,5 mg strength; 20 % of injections for the 30 mg strength and 16 % of injections for the 45 mg strength[3].
- Pain in 4,3 % of injections for the 7,5 mg strength; 3,5 % of injections for the 22,5 mg strength; 2,3 % of injections[2] for the 30 mg strength and 4,6 % of injections for the 45 mg strength[4].
- Erythema in 2,6 % of injections for the 7,5 mg strength; 0,9 % of injections for the 22,5 mg strength[1] and 1,1 % of injections for the 30 mg strength.
- Bruising in 2,5 % of injections for the 7,5 mg strength; 1,7 % of injections for the 22,5 mg strength and 2,3 % of injections for the 45 mg strength[5].
- Pruritis in 1,4 % of injections for the 7,5 mg strength and 0,4 % of injections for the 22,5 mg strength.
- Induration in 0,4 % of injections for the 7,5 mg strength.
- Ulceration in 0,1 % of injections for the 7,5 mg strength.

1. Erythema was reported following 2 injections of ELIGARD 22,5 mg. One report characterised the erythema as mild and it resolved within 7 days. The other report characterised the erythema as moderate and it resolved within 15 days. Neither patient experienced erythema at multiple injections

2. A single event reported as moderate pain resolved within 2 minutes and all 3 mild pain events resolved within several days following injection of ELIGARD 30 mg.

3. Following injection of ELIGARD 30 mg, three of the 35 burning/stinging events were reported as moderate.

4. Transient pain was reported as mild in intensity in 9 of 10 (90 %) events and moderate in intensity in one of ten (10 %) events following injection of ELIGARD 45 mg.

5. Mild bruising was reported following 5 (2,3 %) study injections and moderate bruising as reported following 2 (< 1 %) study injections of ELIGARD 45 mg.

The localised adverse events were non-recurrent over time. No patient discontinued therapy due to an injection site adverse event.

The following possibly or probably related systemic adverse events occurred during clinical trials of up to 6 months of treatment with ELIGARD and were reported in ≥ 2 % of patients. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not product-related are excluded.

***Body as a whole*:**

- Malaise and fatigue occurred in 17, 5 % of patients treated with the 7,5 mg strength; 6 % of patients treated with the 22,5 mg strength; 13,3 % of patients treated with the 30 mg strength and 11,7 % of patients treated with the 45 mg strength.
- Weakness occurred 3,6 % of patients treated with the 45 mg strength.

***Nervous system disorders*:**

- Dizziness occurred in 3,3 % of patients treated with the 7,5 mg strength; and 4,4 % of patients treated with the 30 mg strength.

Vascular disorders:

- Hot flushes/ sweats occurred in 56,7 % of patients treated with the 7,5 mg strength; 56,4 % of patients treated with the 22,5 mg strength; 73,3 % of patients treated with the 30 mg strength and 57,7 % of patients treated with the 45 mg strength.

Renal/ urinary disorders:

- Urinary frequency occurred in 2,6 % of patients treated with the 22,5 mg strength and 2,2 % of patients treated with the 30 mg strength.
- Nocturia occurred in 2,2 % of patients treated with the 30 mg strength.

Gastro-intestinal disorders:

- Nausea occurred in 3,4 % of patients treated with the 22,5 mg strength and 2,2 % of patients treated with the 30 mg strength.

- Gastroenteritis/ colitis occurred in 2,5 % of patients treated with the 7,5 mg strength.

Skin and subcutaneous disorders:

- Pruritis occurred in 2,6 % of patients treated with the 22,5 mg strength.
- Clamminess occurred in 4,4 % of patients treated with the 30 mg strength.
- Night sweats occurred in 3,3 % of patients treated with the 30 mg strength and 2,7 % of patients treated with the 45 mg strength.
- Alopecia occurred in 2,2 % of patients treated with the 30 mg strength.

Musculoskeletal disorders:

- Arthralgia occurred in 3,4 % of patients treated with the 22,5 mg strength.
- Myalgia occurred in 2,2 % of patients treated with the 30 mg strength and 4,5 % of patients treated with the 45 mg strength.
- Pain in limbs occurred in 2,7 % of patients treated with the 45 mg strength.

Reproductive disorders:

- Testicular atrophy occurred in 5,0 % of patients treated with the 7,5 mg strength; 4,4 % of patients treated with the 30 mg strength and 7,2 % of patients treated with the 45 mg strength.
- Gynaecomastia occurred in 2,2 % of patients treated with the 30 mg strength and 3,6 % of patients treated with the 45 mg strength.
- Testicular pain occurred 2,2 % of patients treated with the 30 mg strength.

Psychiatric disorders:

- Decreased libido occurred in 3,3 % of patients treated with the 30 mg strength.

In addition, the following related systemic adverse events were reported by < 2 % of patients treated with ELIGARD:

- *General disorders:* Sweating, insomnia, syncope, rigors, weakness, lethargy
- *Gastrointestinal disorders*: Flatulence, constipation, dyspepsia

1.3.1.1.1 Professional Information for medicines for human use

- *Haematologic disorders*: Decreased red blood cell count, haematocrit and haemaglobin.
- *Metabolic disorders*: Weight gain
- *Musculoskeletal disorder:* Tremor, backache, joint pain, muscle atrophy, limb pain
- *Nervous system disorders:* Disturbance of smell and taste, depression, vertigo
- *Reproductive/Urogenital disorders:* Testicular soreness, impotence*, decreased libido*, gyanecomastia*, breast soreness/ tenderness*, testicular atrophy*, erectile dysfunction, penile disorder*, reduced penis size
- *Skin disorders:* Alopecia, clamminess, night sweats*, increased sweating*
- *Vascular disorders:* Hypertension, hypotension.

*Expected pharmacological consequences of testosterone suppression.

Tabulated list of additional adverse reactions

Body System	**Undesirable effect**					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Infections and Infestations:		nasopharyngitis	urinary tract infection, local skin infection			
Metabolism and nutrition disorders:			aggravated diabetes mellitus			
Psychiatric disorders:			abnormal dreams			
Nervous system disorders:			headache, hypoaesthesia	abnormal involuntary movements		idiopathic intracranial hypertension (pseudotumor

						cerebri) (*see section 4.4*)
Cardiac disorders:						QT prolongation (*see sections 4.4 and 4.5*)
Vascular disorders:				Collapse		
Respiratory, thoracic and mediastinal disorders:			rhinorrhoea ,dyspnoea			interstitial lung disease
Gastrointestinal disorders:		diarrhoea	dry mouth, vomiting	eructation		
Skin and subcutaneous tissue disorders:	ecchymoses			skin eruption		Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic Skin Eruption, Erythema Multiforme
Musculoskeletal, connective tissue and bone disorders:			muscle cramps			
Renal and urinary disorders:		urinary infrequency, difficulty in micturation, dysuria	bladder spasm, haematuria, aggravated urinary frequency, urinary retention			

Reproductive system and breast disorders:		infertility				
General disorders and administrative site conditions:	injection site paraesthesia		pyrexia		injection site necrosis	
Investigations:		increased blood creatinine phosphokinase, prolonged coagulation time	increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time			

Description of selected adverse reactions

- Other adverse events which have been reported in general to occur with ELIGARD 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 medicines in this class. Infarction of pre-existing pituitary apoplexy has been reported rarely after administration of both short and long-acting GnRH agonists such as ELIGARD.
- There have been rare reports of thrombocytopenia and leucopenia.
- Changes in glucose tolerance have been reported.
- Anaphylactic/anaphylactoid reactions have been reported rarely after ELIGARD (GnRH agonist analogue) administration.

Changes in Bone Density:

- Decreased bone density has been reported in the medical literature in men who had orchiectomy or who have been treated with an LH-RH agonist analogue, such as

ELIGARD. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Post-marketing experience:

- Cases of pituitary apoplexy have been reported. In the majority of cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status and sometime cardiovascular collapse. Immediate medical attention has been required.
- Convulsions have been reported after GnRH agonist analogue administration, such as ELIGARD.
- Interstitial lung disease has been reported with an unknown frequency, in post marketing experience.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A26 Cytostatics

Pharmacotherapeutic group and ATC code:

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

Leuprolide acetate is a synthetic non-apeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis.

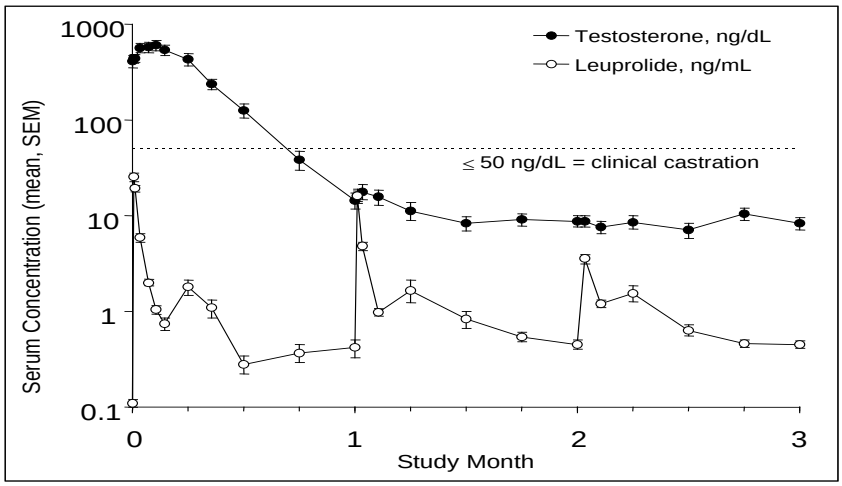
Administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in the levels of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate levels (< 50 ng/dL). These decreases occur within two to four weeks after initiation of treatment. Long-term studies have shown that continuation of therapy maintains testosterone below the castrate level for up to seven years.

5.2 Pharmacokinetic properties

Absorption: The pharmacokinetics/ pharmacodynamics observed during three once monthly subcutaneous injections (ELIGARD 7,5 mg) in 20 patients with advanced carcinoma of the prostate are shown in Figure 1. Mean serum leuprolide concentrations following the initial injection rose to 25,3 ng/ml (C_{max}) at approximately 5 hours after injection. After the initial increase following each injection, serum concentrations remained relatively constant (0,28 – 2,00 ng/ml). There was no evidence of significant accumulation of leuprolide

following repeated dosing. Non-detectable leuprolide plasma concentrations have been observed during chronic ELIGARD 7,5 mg administration, but testosterone levels were maintained at castrate levels.

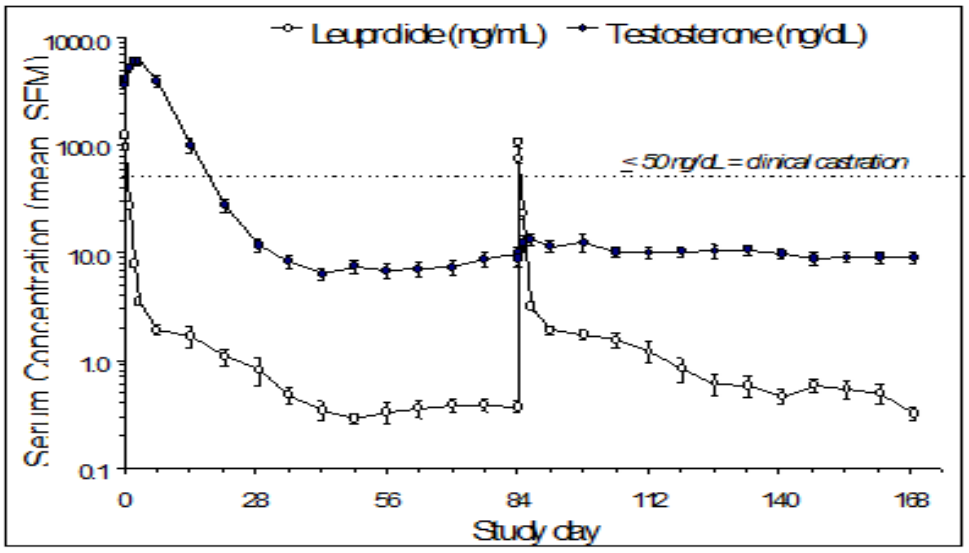
Figure 1: Pharmacokinetic and pharmacodynamic response (N=20) to ELIGARD 7,5 mg – patients dosed initially and at months 1 and 2.



The pharmacokinetics/pharmacodynamics observed during two injections every three months (ELIGARD 22,5 mg) in 22 patients with advanced carcinoma of the prostate is shown in Figure 2. Mean serum leuprolide concentrations rose to 127 ng/mL and 107 ng/mL at approximately 5 hours following the initial and second injections, respectively. After the initial increase following each injection, serum leuprolide concentrations remained relatively constant (0,2 – 2,0 ng/mL). There was no evidence of significant accumulation during repeated dosing. Non-detectable leuprolide plasma concentrations have been observed during chronic ELIGARD 22,5 mg administration, but testosterone levels were maintained at castrate levels.

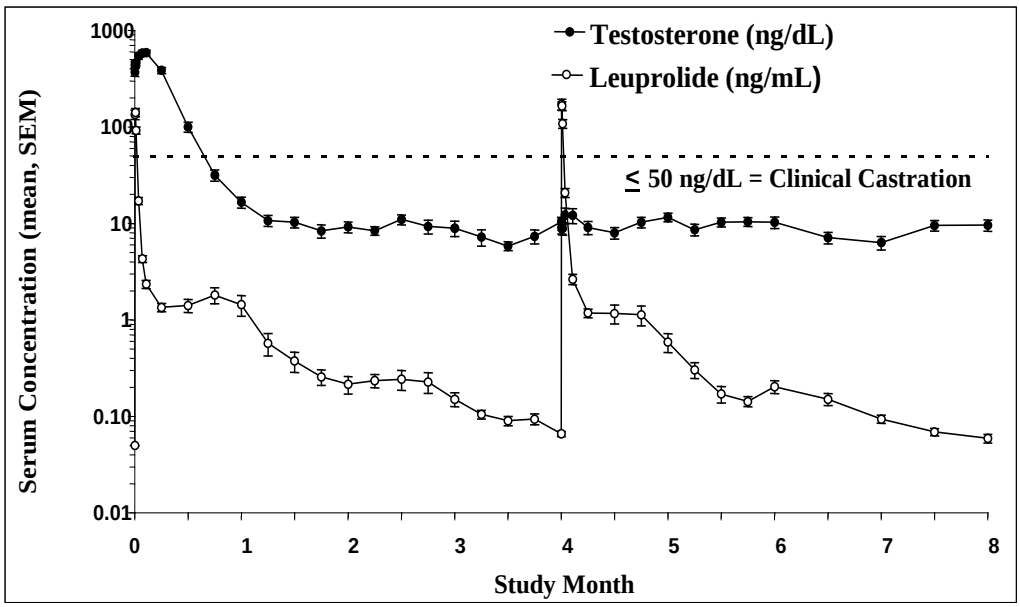
Figure 2: Pharmacokinetic and pharmacodynamic profiles of ELIGARD 22,5 mg, showing serum leuprolide and testosterone levels after two consecutive sc doses, administered at baseline and month 3 (day 84) to advanced prostate cancer patients

(n=22).



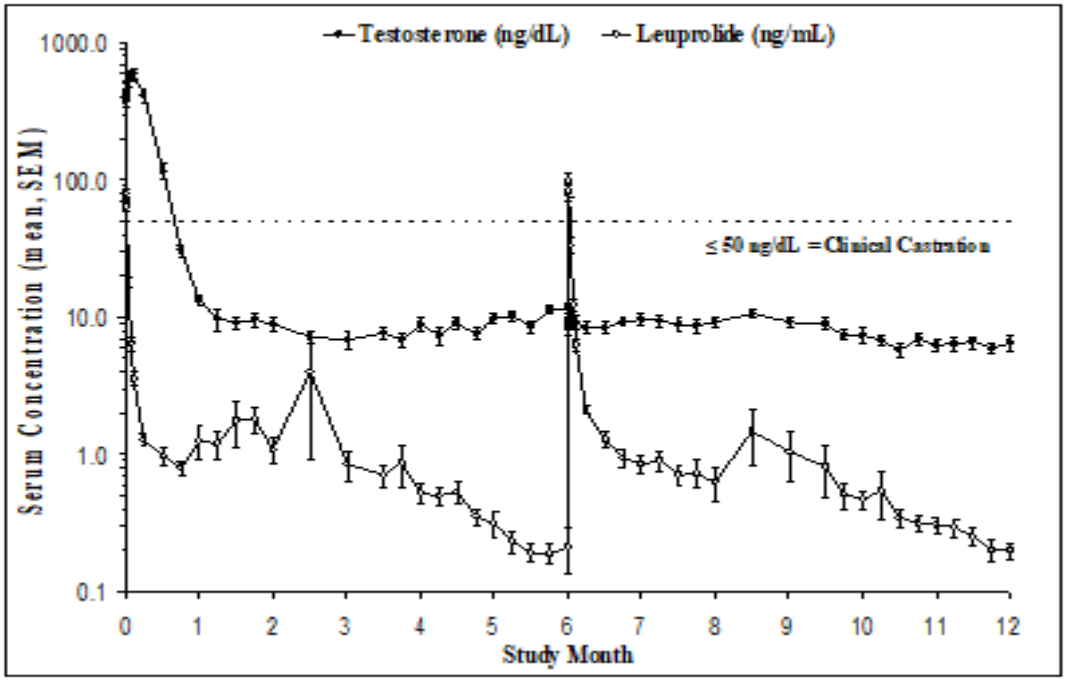
The pharmacokinetics/ pharmacodynamics observed during injections administered initially and at four months (ELIGARD 30 mg) in 24 patients with advanced carcinoma of the prostate are shown in Figure 3. Mean serum leuprolide concentrations following the initial injection rose rapidly to 150 ng/ml (C_{max}) at approximately 3,3 hours after injection. After the initial increase following each injection, mean serum concentrations remained constant (0,1 – 1,0 ng/ml). There was no evidence of significant accumulation of leuprolide following repeated dosing. Non-detectable leuprolide plasma concentrations have been occasionally observed during ELIGARD 30 mg administration, but testosterone levels were maintained at castrate levels.

Figure 3: Pharmacokinetic and pharmacodynamic response (N=24) to ELIGARD 30 mg - patients dosed initially and at 4 months.



The pharmacokinetics/ pharmacodynamics observed during injections administered initially and at six months (ELIGARD 45 mg) in 27 patients with advanced carcinoma of the prostate are shown in Figure 4. Mean serum leuprolide concentrations following the initial injection rose to 82 ng/ml and 102 ng/ml (C_{max}) at approximately 4,5 hours after the initial and second injections, respectively. After the initial increase following each injection, mean serum concentrations remained constant (0,2 – 2,0 ng/ml). There was no evidence of significant accumulation of leuprolide following repeated dosing. Non-detectable leuprolide plasma concentrations have been occasionally observed during ELIGARD 45 mg administration, but testosterone levels were maintained at castrate levels.

Figure 4: Pharmacokinetic and pharmacodynamic response (N=27) to ELIGARD 45 mg - patients dosed initially and at 6 months.



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

Metabolism: In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8,34 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model. The major metabolite of leuprolide acetate is the pentapeptide (M-1) metabolite.

Excretion: No excretion study was conducted with ELIGARD.

Special populations:

Paediatrics: The safety and efficacy of ELIGARD in paediatric patients have not been established.

Renal and hepatic insufficiency: The pharmacokinetics of ELIGARD in hepatically and

renally impaired patients have not been determined.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solvent (Syringe A): Poly (DL-lactic-co-glycolic-acid); N-Methylpyrrolidone

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in the original packaging material under refrigerated conditions (2 °C to 8 °C).

Once outside the refrigerator this product may be stored in its original packaging at or below 25 °C for up to eight weeks prior to constitution.

Do not remove from the outer carton until required for use.

Store in the original package/container.

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.

1.3.1.1.1 Professional Information for medicines for human use

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 18-gauge or 20-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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

For handling of the product please refer to section 4.2 ‘Method of administration’.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

ELIGARD ® 7,5 mg: A39/26/0648

ELIGARD ® 22,5 mg: A39/26/0649

ELIGARD ® 45 mg: A39/26/0651

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2008

10 DATE OF REVISION OF TEXT

23 July 2025