

## **AUSTRALIAN PRODUCT INFORMATION**

### **ELIGARD® (LEUPRORELIN ACETATE) MODIFIED RELEASE INJECTION SYRINGE**

#### **1 NAME OF THE MEDICINE**

Leuporelin acetate

#### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

ELIGARD is a sterile polymeric matrix formulation of leuporelin acetate for subcutaneous injection. It is designed to deliver leuporelin acetate at a controlled rate over a therapeutic period.

Leuporelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis. The analogue possesses greater potency than the natural hormone.

ELIGARD 1 month contains 10.6 mg of lyophilised leuporelin acetate. ELIGARD 1 month delivers 7.5 mg of leuporelin acetate (equivalent to approximately 7.0 mg leuporelin free base) dissolved in 160 mg N-methyl-2-pyrrolidone and 82.5 mg polyglactin. The approximate weight of the administered formulation is 250 mg. It is designed to deliver 7.5 mg of leuporelin acetate at a controlled rate over a 1 month therapeutic period.

ELIGARD 3 month contains 29.2 mg lyophilised leuporelin acetate. ELIGARD 3 month delivers 22.5 mg of leuporelin acetate (equivalent to approximately 21 mg leuporelin free base) dissolved in 193.9 mg N-methyl-2-pyrrolidone and 158.6 mg polyglactin. The approximate weight of the administered formulation is 375 mg. It is designed to deliver 22.5 mg of leuporelin acetate at a controlled rate over a 3 month therapeutic period.

ELIGARD 4 month contains 37.2 mg lyophilised leuporelin acetate. ELIGARD 4 month delivers 30 mg of leuporelin acetate (equivalent to approximately 28 mg leuporelin free base) dissolved in 258.5 mg N-methyl-2-pyrrolidone and 211.5 mg polyglactin. The approximate weight of the administered formulation is 500 mg. It is designed to deliver 30 mg of leuporelin acetate at a controlled rate over a 4 month therapeutic period.

ELIGARD 6 month contains 59.2 mg of lyophilised leuporelin acetate. ELIGARD 6 month delivers 45 mg of leuporelin acetate (equivalent to approximately 42 mg leuporelin free base) dissolved in 165 mg N-methyl-2-pyrrolidone and 165 mg polyglactin. The approximate weight of the administered formulation is 375 mg. It is designed to deliver 45 mg of leuporelin acetate at a controlled rate over a 6 month therapeutic period.

The Atrigel® Delivery System is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable polyglactin. The polymer is dissolved in a biocompatible solvent,

N-methyl-2-pyrrolidone. The polyglactin mixture and volume differ with each presentation of ELIGARD.

ELIGARD contains no anti-microbial agent. ELIGARD does not contain: lactose, sucrose, gluten, tartrazine, or any other azo dyes.

### 3 PHARMACEUTICAL FORM

ELIGARD is a modified release suspension syringe, available in a single use kit.

ELIGARD is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. ELIGARD is administered subcutaneously where it forms a solid drug delivery depot.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

ELIGARD is indicated for the:

- Palliative treatment of advanced prostate cancer.
- Treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy.<sup>1</sup>

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

**IMPORTANT:** Allow the product to reach room temperature before using. **Once mixed, ELIGARD must be administered within 30 minutes.** Discard the constituted product if not administered within 30 minutes.

The two syringes are coupled and the product is mixed by transferring the contents from syringe to syringe immediately before administration to the patient. Refer to the enclosed leaflet titled ELIGARD Mixing Procedure. The syringes are uncoupled and the needle is attached prior to injection. The product is injected subcutaneously into areas with adequate amounts of subcutaneous tissue (such as the abdomen) and that do not have excessive pigment, nodules, lesions, or hair. As with other drugs administered by subcutaneous injection, the injection site should be varied periodically.

When thoroughly mixed, the suspension will appear a light tan to tan colour (ELIGARD 1 month) or a colourless to pale yellow colour (ELIGARD 3 month, ELIGARD 4 month and ELIGARD 6 month). The mixed solution colour is not representative of product quality. An occasional slightly grey appearance of the mixed solution may be due to tiny air bubbles and will not affect the product quality.

ELIGARD should not be injected in the arm.

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<sup>1</sup> Not indicated for BI ELIGARD® CP combination pack

The recommended dose of ELIGARD 1 month is one injection every month.  
The recommended dose of ELIGARD 3 month is one injection every three months.  
The recommended dose of ELIGARD 4 month is one injection every four months.  
The recommended dose of ELIGARD 6 month is one injection every six months.

ELIGARD 1, 3, 4 and 6 month presentations have different release characteristics and therefore, fractional, multiple and/or combinational doses are not equivalent to each other and should not be given.

ELIGARD contains no antimicrobial agent and is for single use in one patient only. Discard any residue.

The injection delivers leuporelin acetate, incorporated in a polymer formulation. It is administered subcutaneously and provides continuous release of leuporelin for one month for ELIGARD 1 month, three months for ELIGARD 3 month, four months for ELIGARD 4 month and six months for ELIGARD 6 month.

#### **4.3 CONTRAINDICATIONS**

ELIGARD is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogues or any of the components of ELIGARD. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogues have been reported in the literature.

ELIGARD is contraindicated in women who are breastfeeding, pregnant or intending to become pregnant and in paediatric patients. ELIGARD was not studied in women or children. Moreover, leuporelin acetate can cause foetal harm when administered to a pregnant woman. Major foetal abnormalities were observed in rabbits but not in rats after administration of leuporelin acetate throughout gestation. There were 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 this drug. The possibility exists that spontaneous abortion may occur.

ELIGARD is contraindicated 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). ELIGARD is contraindicated as a sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastases.

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

ELIGARD, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone 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. Isolated cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been observed in the palliative treatment of advanced prostate cancer using LH-RH agonists.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuporelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients (e.g. those with thecal

indentation, or at risk of cord compression, and patients with bladder neck obstruction). Additional administration of an appropriate antiandrogen should be considered beginning 3 days prior to leuporelin 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.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Long-term administration of leuporelin will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

### **General**

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

Response to ELIGARD should be monitored by measuring serum concentrations of testosterone and prostate-specific antigen periodically.

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.

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

A proportion of patients will have tumors which are not sensitive to hormone manipulation. This is termed castrate-resistant prostate cancer. Signs and/or symptoms of tumor progression despite adequate testosterone suppression are diagnostic of this condition. Current treatment paradigms recommend continued GnRH therapy along with other therapeutic regimens for this circumstance.

### **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.

### **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 a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

### **Effect on QT/QTc Interval**

Androgen deprivation therapy may prolong the QT interval. Physicians 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 drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

### **Changes in Bone Density**

Bone loss can be expected as part of natural aging and can also be anticipated during the hypoandrogenic state caused by long-term use of leuporelin acetate. In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic abuse of alcohol or tobacco, leuporelin acetate may pose additional risk. In these patients, risk versus benefit must be weighed carefully before initiation of leuporelin acetate therapy.

### **Convulsions**

Post marketing reports of convulsions have been observed in patients on leuporelin acetate therapy with or without a history of predisposing factors. These included patients in the female and paediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumours, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Convulsions are to be managed according to the current clinical practice.

### **Respiratory**

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

### **Use in hepatic impairment**

ELIGARD was not studied in hepatically and renally impaired patients.

### **Use in renal impairment**

ELIGARD was not studied in hepatically and renally impaired patients.

### **Use in the elderly**

The majority of the patients (approximately 70%) studied in the clinical trials were age 70 and older.

### **Paediatric use**

The safety and effectiveness of ELIGARD in paediatric patients have not been established (see Section 4.3 - Contraindications).

### **Effects on laboratory tests**

In the majority of non-orchietomised patients, testosterone levels increased during the first week of treatment. They then decreased and by day 14 had returned to baseline levels or below. Castrate levels were reached in 2 to 4 weeks. Once achieved, castrate levels were maintained as long as the patient received their injections. Transient increases in acid

phosphatase levels may occur early in the treatment period; however, by the fourth week the elevated levels usually decreased to values at or near normal. Therapy with leuporelin results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuporelin therapy may be affected.

#### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

There are no reports of drug interactions with leuporelin acetate to date.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ELIGARD 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) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see Section 4.4 Special warnings and precautions for use).

#### **4.6 FERTILITY, PREGNANCY AND LACTATION**

##### **Effects on fertility**

Preclinical studies with leuporelin acetate in rats demonstrated reversible, expected effects (given that leuporelin acetate has known pharmacological effects on reproductive endocrinology) on the reproductive system of both sexes.

Leuporelin acetate did not show teratogenicity in rats.

Clinical and pharmacological studies in adults with leuporelin acetate and similar analogues have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

##### **Use in pregnancy - Pregnancy Category D**

(See Section 4.3 Contraindications).

Although not relevant to the approved indication, leuporelin acetate is contraindicated in pregnancy due to its embryotoxic effects.

##### **Use in lactation**

ELIGARD is contraindicated for use in breastfeeding women.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

#### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

ELIGARD, like other LH-RH analogues, caused a transient increase in serum testosterone concentrations during the first two weeks of treatment. Therefore, potential exacerbations 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 (see Section 4.4 Special warnings and precautions for use).

'Flare' Phenomenon: The initial increase in circulating levels of pituitary gonadotropins and gonadal steroids leads in some patients to a transient exacerbation of symptoms and signs ('flare' phenomenon). The exacerbation may include worsened bone pain, ureteric obstruction and spinal cord compression. This possibility should be taken into account in deciding to initiate leuporelin acetate therapy in patients with existing obstructive uropathy or vertebral metastases. Early symptoms of spinal cord compression such as paraesthesia should alert the physician to the need for intensive monitoring and possible treatment.

There is no information available on the clinical effects of interrupting leuporelin acetate therapy and whether this will produce a withdrawal 'flare'.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuporelin acetate therapy has proven benefit in reducing flare reactions in 'at risk' patients.

The safety of ELIGARD was evaluated in open-label, multicentre studies. In ELIGARD clinical studies conducted, patient injection sites were closely monitored. The adverse reactions from injections sites are summarised in Table 1.

**Table 1:** Summary of adverse reactions from ELIGARD injection sites

<b>Presentation</b>	<b>ELIGARD 1 month</b>	<b>ELIGARD 3 month</b>	<b>ELIGARD 4 month</b>	<b>ELIGARD 6 month</b>
Total number of injections (N=)	716	230	175	217
Adverse reactions (% of injections)				
Transient burning/stinging	34.6	21.7	20	16
Pain	4.3	3.5	2.3	4.6
Erythema	2.6	0.9	1.1	–
Mild bruising	2.5	1.7	–	2.3
Pruritis	1.4	0.4	–	–
Induration	0.4	–	–	–
Ulceration	0.1	–	–	–

The majority (84%) of transient burning/stinging events for ELIGARD 1 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. Erythema were all reported as mild and generally resolved within a few days post-injection.

The majority (86%) of transient burning/stinging events for ELIGARD 3 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. One of the reports characterized the erythema as mild and resolved within 7 days. The other was moderate and resolved within 15 days. Neither patient experienced erythema at multiple injections.

All (100%) of transient burning/stinging events for ELIGARD 4 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. Erythema was reported as mild in all cases and generally resolved within a few days post-injection.

The majority (91%) of transient burning/stinging events for ELIGARD 6 month were reported as mild. Pain was generally reported as brief in duration and mild in intensity. Mild bruising was reported following five (2.3%) study injections and moderate bruising was reported following two (<1%) study injections.

The following possibly or probably related systemic adverse events occurred during clinical trials of up to six months of treatment with ELIGARD 1 month and ELIGARD 3 month, up to eight months of treatment with ELIGARD 4 month and up to 12 months of treatment with ELIGARD 6 month, and were reported in  $\geq 2\%$  and  $< 2\%$  of patients (Tables 2 and 3, respectively). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related were excluded.

### More Common Reactions (incidence $\geq 2\%$ )

**Table 2:** Incidence (%) of Possibly Related Systemic Adverse Events Reported by  $\geq 2\%$  of Patients Treated with ELIGARD 1 month and ELIGARD 3 month for up to six months, ELIGARD 4 month up to eight months and ELIGARD 6 month up to 12 months

	<b>Adverse Event</b>	<b>ELIGARD 1 month<sup>1</sup></b> <b>N (%)</b>	<b>ELIGARD 3 month<sup>2</sup></b> <b>N (%)</b>	<b>ELIGARD 4 month<sup>2</sup></b> <b>N (%)</b>	<b>ELIGARD 6 month<sup>2</sup></b> <b>N (%)</b>
Body as a Whole	Malaise and Fatigue *	21 (17.5%)	7 (6.0 %)	12 (13.3%)	13 (11.7)
	Weakness				4 (3.6%)
	Dizziness	4 (3.3%)	-	4 (4.4 %)	-
Cardiovascular	Hot flashes/sweats*	68 (56.7%)	66 (56.4%)	66 (73.3%)	64 (57.7)
Genitourinary	Atrophy of Testes *	6 (5.0%)	-	4 (4.4%)	8 (7.2)
	Nocturia	-	-	2 (2.2 %)	-
	Urinary frequency	-	3 (2.6 %)	2 (2.2 %)	-
Digestive	Gastroenteritis/Colitis	3 (2.5%)	-	-	-
	Nausea	-	4 (3.4 %)	2 (2.2 %)	-
Reproductive	Gynaecomastia *	-	-	2 (2.2 %)	4 (3.6)
	Testicular pain	-	-	2 (2.2 %)	-
Skin	Clamminess *	-	-	4 (4.4 %)	-
	Night sweats *	-	-	3 (3.3 %)	3 (2.7)
	Alopecia	-	-	2 (2.2 %)	-
	Pruritis	-	3 (2.6 %)	-	-
Psychiatric	Decreased libido *	-	-	3 (3.3 %)	-
Musculoskeletal	Myalgia	-	-	2 (2.2 %)	5 (4.5)
	Arthralgia	-	4 (3.4 %)	-	
	Pain in limb				3 (2.7)

<sup>1</sup> adverse events are classified using ICD-9 terms

<sup>2</sup> adverse events are classified using MedDRA terms

\* Expected pharmacological consequences of testosterone suppression.

## Less Common Reactions (incidence < 2%)

**Table 3:** Possibly or Probably Related Systemic Adverse Events Reported by < 2% of Patients Treated with ELIGARD 1 month<sup>1</sup> and ELIGARD 3 month<sup>2</sup> for up to six months, ELIGARD 4 month<sup>2</sup> up to eight months and ELIGARD 6 month<sup>2</sup> for up to 12 months

Body System	Adverse Event
General	Sweating*, insomnia, syncope, rigors, weakness, lethargy
Gastrointestinal	Flatulence, constipation, dyspepsia
Haematologic	Decreased red blood cell count, haematocrit and haemoglobin
Metabolic	Weight gain
Musculoskeletal	Tremor, backache, joint pain, muscle atrophy, limb pain
Nervous	Disturbance of smell and taste, depression, vertigo
Psychiatric	Insomnia, depression, loss of libido*
Skin	Alopecia, clamminess, night sweats*, sweating increased*
Urogenital / Reproductive	Decreased libido*, gynaecomastia*, breast tenderness*, testicular atrophy*, testicular pain, erectile dysfunction*, penis disorder*, reduced penile size*
Renal and urinary disorders	Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine and urinary retention, urinary urgency, incontinence, nocturia, urinary tract infection
Vascular	Hypertension, hypotension

<sup>1</sup> adverse events are classified using ICD-9 terms

<sup>2</sup> adverse events are classified using MedDRA terms

\* Expected pharmacological consequence of testosterone suppression.

### ELIGARD in combination with radiotherapy

The addition of ADT in the form of leuporelin acetate to radiotherapy unequivocally resulted in an increased range of acute and late toxicities. Some of these pivotal studies employed half of the currently recommended dose of leuporelin. Long term safety data on the combination therapy was limited due to long term use of an anti-androgen in some studies, but limited use of leuporelin.

### Post-marketing experiences

#### *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 gonadotropin releasing hormone agonists, with a majority occurring within two weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as a sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

#### *Other Adverse Effects*

During post-market surveillance with LH-RH agonists; diabetes mellitus, myocardial infarction, cerebrovascular accident and sudden cardiac death have also been reported (see Section 4.4 Special warnings and precautions for use).

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

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

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

Interstitial lung disease has been reported with an unknown frequency.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

In clinical trials using daily subcutaneous leuprorelin acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

There is no clinical experience with the effects of an acute overdose. Because the acute animal toxicity of the drug is low, adverse effects are not expected. In the event of an overdose the patient should be monitored and supportive treatment given, if considered necessary.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

Leuprorelin acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprorelin acetate results in suppression of testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone-dependent tumours (prostatic tumours in Noble and Dunning male rats and DMBA-induced mammary tumours in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprorelin acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and oestrone and oestradiol in premenopausal females). However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold ( $\leq 50$  ng/dL). These decreases occur within two to six weeks after initiation of treatment.

Leuprorelin acetate is not active when given orally.

### Clinical trials

In the open-label, multicentre studies conducted with ELIGARD patients with advanced prostate cancer were treated with monthly injections of ELIGARD 1 month for 6 months, a single injection of ELIGARD 3 month, given once every three months for 6 months, a single injection of ELIGARD 4 month, given once every four months for 8 months or a single injection of ELIGARD 6 month, given once every six months for 12 months. Patient stages in the open-label, multicentre studies are described in Table 4. The ELIGARD 1 month and ELIGARD 3 month studies evaluated the achievement and maintenance of serum testosterone suppression over six months of therapy. The ELIGARD 4 month study evaluated the achievement and maintenance of serum testosterone suppression over eight months of therapy. The ELIGARD 6 month study evaluated the achievement and maintenance of serum testosterone suppression over twelve months of therapy.

**Table 4:** Description of patients in open-label, multicentre studies for ELIGARD

Presentation	Total	Stage A disease	Stage B disease	Stage C disease	Stage D disease
ELIGARD 1 month	120	0	0	89	31
ELIGARD 3 month	117	2	19	60	36
ELIGARD 4 month	90	2	38	16	34
ELIGARD 6 month	111	5	43	19	44

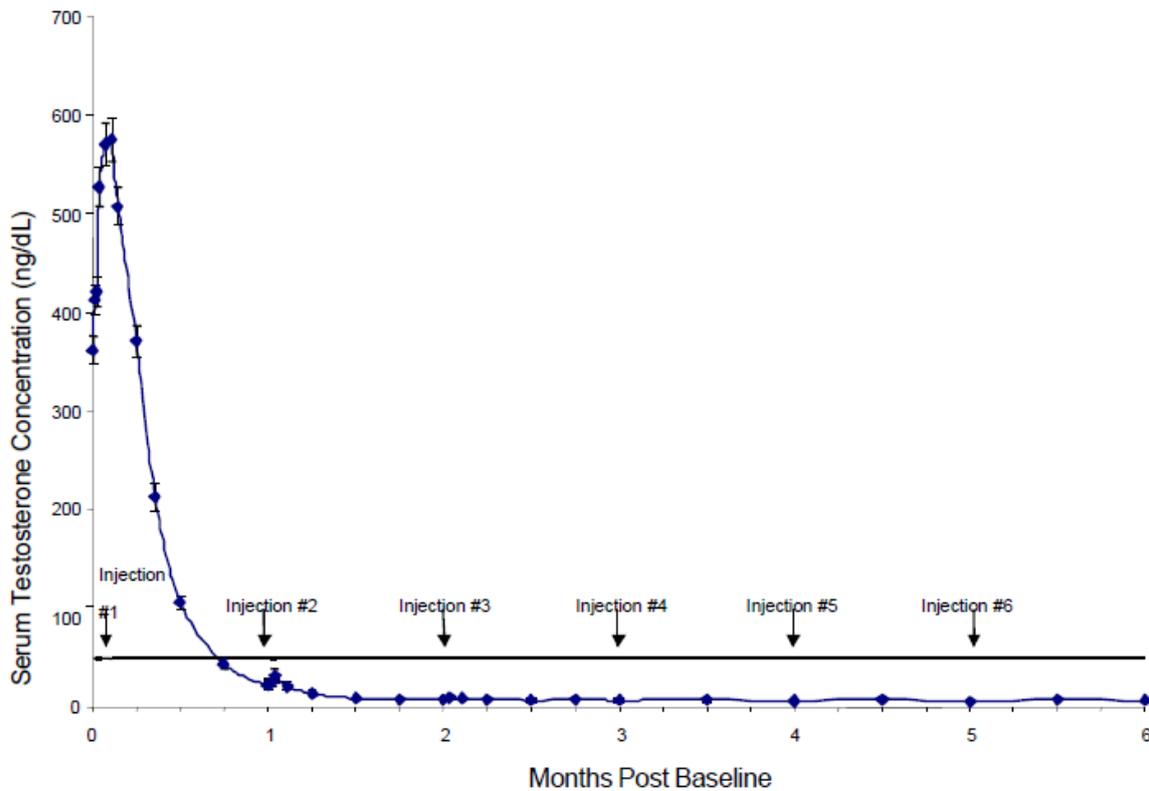
Patients with brain metastases, spinal cord compression and/or urinary tract obstruction, serum testosterone levels below 150 ng/dL at screening, uncontrolled congestive heart failure, myocardial infarction or a coronary vascular procedure, symptomatic cardiovascular disease, venous thrombosis, uncontrolled hypertension, symptomatic hypotension, insulin dependent diabetes, a history of drug and alcohol abuse, other serious intercurrent illness, (for example, haematological, renal hepatic, respiratory, endocrine) were excluded from the studies.

#### *ELIGARD 1 month*

The mean testosterone concentration increased from 361.3 ng/dL at baseline to 574.6 ng/dL at day 3 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below baseline by day 10 and was 21.8 ng/dL on day 28. At the conclusion of the study (month 6), mean testosterone concentration was 6.1 ng/dL (Figure 1a), comparable to levels following bilateral orchiectomy.

Serum testosterone was suppressed to below the castrate threshold ( $\leq 50$  ng/dL) by day 28 (week 4) in 112 of 119 (94.1%) patients remaining in the study. The remaining seven patients all attained the castrate threshold by day 42. A high proportion of patients (97% at day 42), achieved testosterone suppression levels of  $\leq 20$  ng/dL, although the full benefit of these low levels has not yet been established. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, no patients (0%) demonstrated breakthrough (concentration above 50 ng/dL) at any time in the study. All 117 evaluable patients in the study

at month 6 (two patients withdrew for reasons unrelated to drug) had testosterone concentrations of  $\leq 50$  ng/dL.

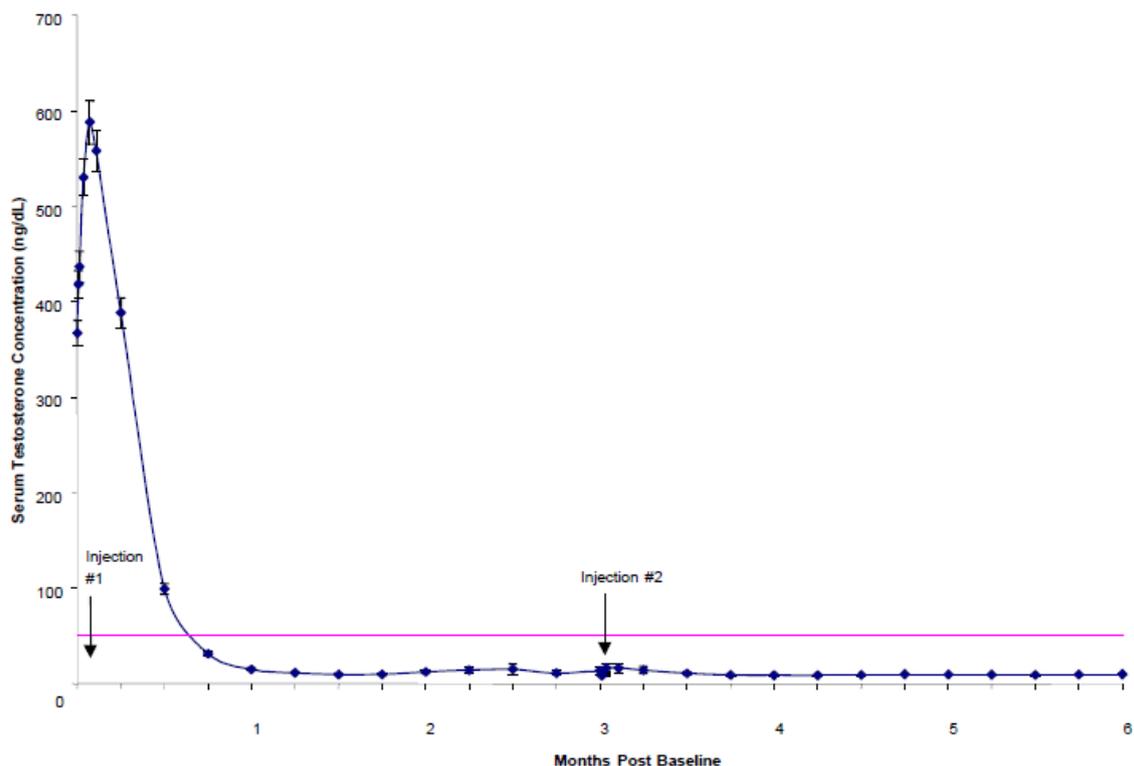


**Figure 1 a:** ELIGARD 1 month mean serum testosterone concentrations (n = 117)

### *ELIGARD 3 month*

The mean testosterone concentration increased from 367.1 ng/dL at baseline to 588.0 ng/dL at day 2 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below baseline by day 14 and was 27.7 ng/dL on day 21. At the conclusion of the study (month 6), mean testosterone concentration was 10.1 ng/dL (Figure 1b), comparable to levels following bilateral orchiectomy.

Of the original 117 patients, one received less than a full dose of ELIGARD 3 month at baseline, never suppressed, and was withdrawn at day 73 and given an alternate treatment. In the remaining 116 patients who did receive the full dose at baseline, serum testosterone was suppressed to below the castrate threshold ( $\leq 50$  ng/dL) by day 28 (week 4) in 115 of 116 (99%). By day 35, all 116 patients (100%) who received a full dose at baseline attained the castrate threshold. A high proportion of patients (84% at day 28 and 92% at day 42), achieved testosterone suppression levels of  $\leq 20$  ng/dL, although the full benefit of these low levels has not yet been established. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, only one patient (<1%) demonstrated breakthrough (concentration above 50 ng/dL) following initial injection; that patient remained below the castrate threshold following the second injection. All 111 evaluable patients in the study at month 6 had testosterone concentrations of  $\leq 50$  ng/dL.

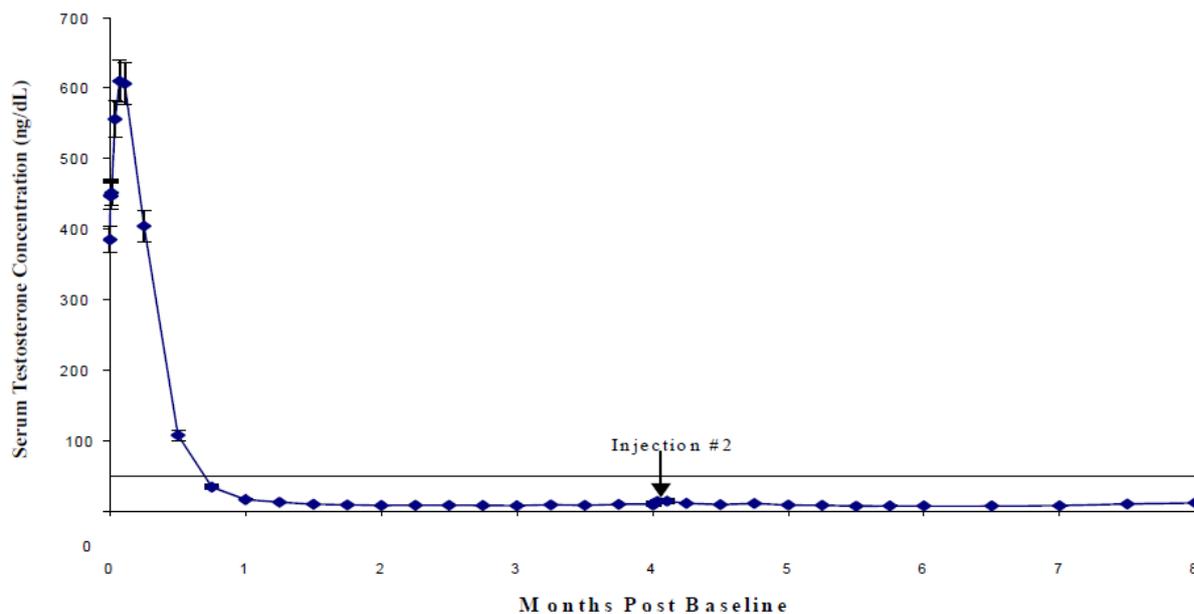


**Figure 1 b:** ELIGARD 3 month mean serum testosterone concentrations (n = 111)

#### *ELIGARD 4 month*

The mean testosterone concentration increased from 385.5 ng/dL at baseline to 610.0 ng/dL at day 2 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below baseline by day 14 and was 17.2 ng/dL on day 28. At the conclusion of the study (month 8), mean testosterone concentration was 12.4 ng/dL (Figure 1c), comparable to levels following bilateral orchiectomy.

Serum testosterone was suppressed to below the castrate threshold ( $\leq 50$  ng/dL) by day 28 in 85 of 89 (96%) patients remaining in the study. All 89 (100%) of patients remaining in the study attained the castrate threshold by day 42. A high proportion of patients (67% at day 28 and 90% at day 42), achieved testosterone suppression levels of  $\leq 20$  ng/dL, although the full benefit of these low levels has not yet been established. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, three patients (3%) demonstrated breakthrough (concentration above 50 ng/dL) during the study. These patients again reached castrate suppression following the second injection of study drug. Of 82 evaluable patients in the study at month 8, 81 had testosterone concentrations of  $\leq 50$  ng/dL.



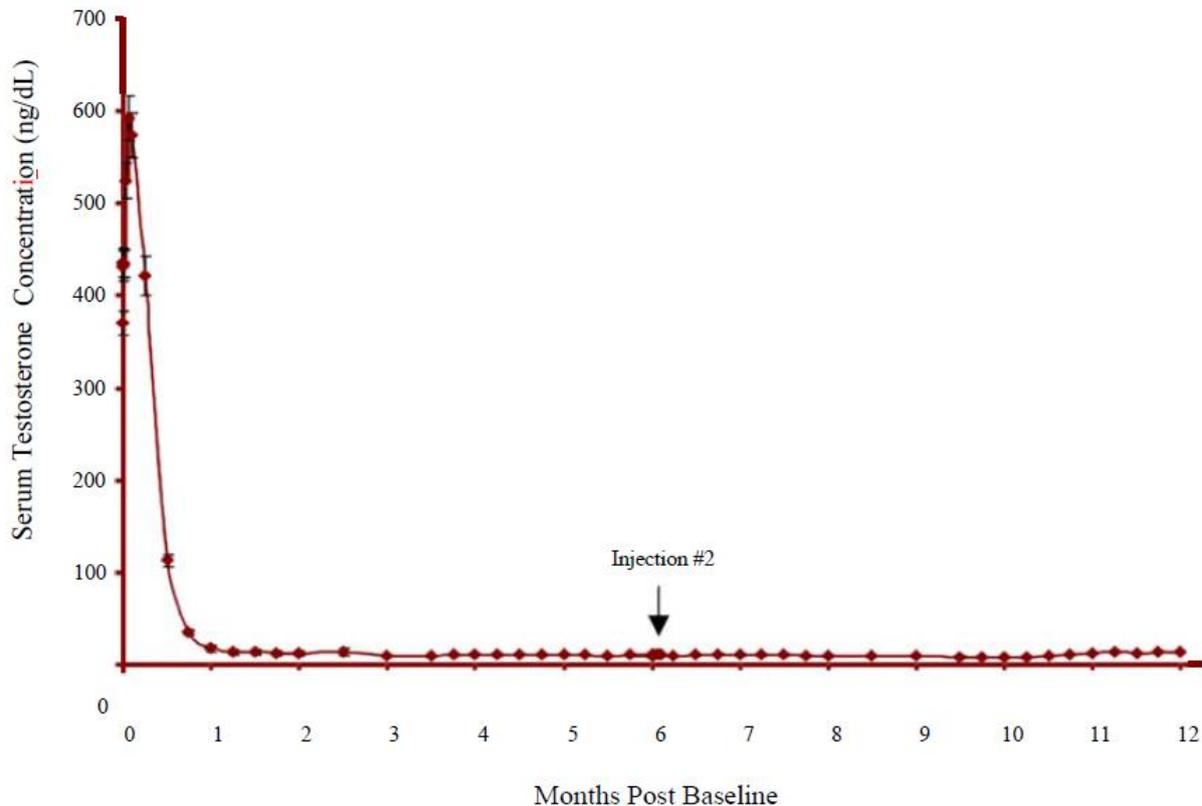
**Figure 1 c:** ELIGARD 4 month mean serum testosterone concentrations (n = 90)

#### *ELIGARD 6 month*

The mean testosterone concentration increased from 367.7 ng/dL at baseline to 588.6 ng/dL at day 2 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below baseline by day 14 and was 16.7 ng/dL on day 28. At the conclusion of the study (month 12), mean testosterone concentration was 12.6 ng/dL (Figure 1d), comparable to levels following bilateral orchiectomy.

Serum testosterone was suppressed to below the castrate threshold ( $\leq 50$  ng/dL) by day 28 in 108 of 109 (99%) patients remaining in the study. One patient (<1%) did not achieve castrate suppression and was withdrawn from the study on day 85. A high proportion of patients remaining in the study (84% at day 28 and 95% at day 42), achieved testosterone suppression levels of  $\leq 20$  ng/dL, although the full benefit of these low levels has not yet been established. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, one patient (<1%) demonstrated breakthrough (concentration above 50 mg/dL) during the study. This patient reached castrate suppression at day 21 and remained suppressed until day 308 when his testosterone level rose to 112 ng/dL. At month 12, his testosterone was 210 ng/dL. Of 103 evaluable patients in the study at month 12, 102 had testosterone concentrations of  $\leq 50$  ng/dL.

All five non-evaluable patients who had achieved castration by day 28 maintained castration at each timepoint, up to and including the time of withdrawal.



**Figure 1 d:** ELIGARD 6 month mean serum testosterone concentrations (n = 103)

Serum PSA decreased in all patients whose baseline values were elevated above the normal limit. Mean values were reduced 94% from baseline to month 6 for ELIGARD 1 month, 98% from baseline to month 6 for ELIGARD 3 month, 86% from baseline to month 8 for ELIGARD 4 month and 97% from baseline to month 12 for ELIGARD 6 month.

At month 6, PSA levels had decreased to within normal limits in 94% of patients who presented with elevated levels at baseline for ELIGARD 1 month. At month 6, PSA levels had decreased to within normal limits in 91% of patients who presented with elevated levels at baseline for ELIGARD 3 month. At month 8, PSA levels had decreased to within normal limits in 93% of patients who presented with elevated levels at baseline for ELIGARD 4 month. At month 12, PSA levels had decreased to within normal limits in 95% of patients who presented with elevated levels at baseline for ELIGARD 6 month.

Other secondary efficacy endpoints evaluated included WHO performance status, bone pain, urinary pain and urinary signs and symptoms.

At baseline, 88% of patients using ELIGARD 1 month, 94% of patients using ELIGARD 3 month, 90% of patients using ELIGARD 4 month and 90% of patients using ELIGARD 6 month were classified as “fully active” by the WHO performance status scale (Status=0). Eleven percent of patients using ELIGARD 1 month, 6% of patients using ELIGARD 3 month, 10% of patients using ELIGARD 4 month and 7% of patients using ELIGARD 6 month were “restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature” (Status=1).

Three percent of patients using ELIGARD 6 month were classified as “ambulatory but unable to carry out work activities” (Status 2).

These percentages were unchanged at month 6 for ELIGARD 1 month. At month 6, 96% of patients using ELIGARD 3 month, 87% of patients using ELIGARD 4 month at month 8 and 94% of patients using ELIGARD 6 month at month 12 were classified as “fully active” by the WHO performance status scale (Status=0). Four percent of patients using ELIGARD 3 month at month 6, 12% of patients using ELIGARD 4 month at month 8 and 5% of patients using ELIGARD 6 month at month 12 were “restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature” (Status=1). One percent of patients using ELIGARD 4 month at month 8 and 1% of patients using ELIGARD 6 month at month 12 were “ambulatory but unable to carry out work activities” (Status 2).

At baseline and at month 6 for ELIGARD 1 month and ELIGARD 3 month, at month 8 for ELIGARD 4 month and at month 12 for ELIGARD 6 month, patients experienced little bone pain. Urinary pain was also low both at baseline and at month 6, 8 or 12, respectively. Urinary signs and symptoms were similarly low at baseline and decreased modestly for ELIGARD 1 month, ELIGARD 4 month, and ELIGARD 6 month at month 6, 8 or 12, respectively. Urinary signs and symptoms were similarly low at baseline and increase modestly for ELIGARD 3 month at month 6. In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 102 (85%) at Screening to 77 (64%) at month 6 for ELIGARD 1 month, from 96 (82%) at Screening to 76 (65%) at month 6 for ELIGARD 3 month, from 66 (73%) at Screening to 54 (60%) at month 8 for ELIGARD 4 month and from 89 (80%) at Screening to 60 (58%) at month 12 for ELIGARD 6 month.

#### *ELIGARD in combination with radiotherapy*

Evidence for the indication of high-risk localised prostate cancer is based on published studies of radiotherapy combined with androgen deprivation therapy (ADT). The ADT included LH-RH agonists, including leuprorelin acetate given at various dosing regimens in the neoadjuvant, concomitant and adjuvant settings, but also clinical experience of nonsteroidal antiandrogens as well as surgical castration.

Clinical data from 8 published studies was analysed for efficacy (Mottet et al., Eur Urol. 2012, Widmark et al., Lancet 2009, Heymann et al., J Clin Oncol. 2007, Solberg et al., I J Radiation Oncol. Biol. Phys. 2011, Nguyen et al., Cancer 2013, Stone et al., Mol Urol. 2000, Stone et al., Mol Urol. 1999, Zelefsky et al., Urology 1997) which demonstrated a clinical benefit for the combination of ADT with radiotherapy, compared to ADT alone. Clear differentiation of the respective study populations for the indications of locally advanced prostate cancer and high-risk prostate cancer was not possible in all the published studies.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

The absorption pharmacokinetic parameters determined for ELIGARD are presented in Table 5.

**Table 5:** Absorption pharmacokinetic parameters for ELIGARD

Presentation of ELIGARD	C <sub>max</sub> ± SD (ng/mL)	T <sub>max</sub> ± SD (hours)
1 month	25.3 ± 11.3	4.7 ± 1.4
3 month *	127 ± 39	4.6 ± 1.6
3 month**	107 ± 50	4.5 ± 1.5
4 month *	150 ± 77	3.3 ± 1.2
4 month**	192 ± 107	3.0 ± 1.0
6 month	102.4 ± 72.1	4.75 ± 2.0

\* first dose

\*\* second dose

After the initial increase following each injection, mean serum concentrations remained relatively constant; 0.28 – 2.0 ng/mL for ELIGARD 1 month, 0.2 – 2.0 ng/mL for ELIGARD 3 month, 0.1 – 1.0 ng/mL for ELIGARD 4 month and 0.2 – 2.0 ng/mL for ELIGARD 6 month. There was no evidence of significant accumulation during repeated dosing. Non-detectable leuprorelin serum concentrations have been observed during chronic ELIGARD administration, but testosterone levels were maintained at castrate levels.

### Distribution

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

### Metabolism

In healthy male volunteers, a 1 mg bolus of leuprorelin administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

Drug metabolism studies were not conducted with ELIGARD. Upon administration with different leuprorelin acetate formulations, the major metabolite of leuprorelin acetate is a pentapeptide (M-1) metabolite.

### Excretion

Drug excretion studies were not conducted with ELIGARD.

### Special populations

#### *Geriatrics*

The majority of the patients (approximately 70%) studied in these clinical trials were age 70 and older.

#### *Paediatrics*

The safety and effectiveness of ELIGARD in paediatric patients have not been established (see Section 4.3 CONTRAINDICATIONS).

### *Renal and hepatic insufficiency*

The pharmacokinetics of ELIGARD in hepatically and renally impaired patients have not been determined.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

Mutagenicity studies have been performed with leuporelin acetate using bacterial and mammalian systems and with ELIGARD 1 month in bacterial systems. These studies provided no evidence of a genotoxic potential.

### **Carcinogenicity**

Two-year carcinogenicity studies were conducted with leuporelin acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuporelin acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuporelin acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Refer to Section 2 - Qualitative and quantitative composition.

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

ELIGARD should be stored below 8°C (refrigerate). The patient may store ELIGARD below 25°C in intact packaging for a period of 8 weeks prior to administration.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

ELIGARD is available in a single use kit. The kit consists of a two-syringe mixing system, a 20-gauge 5/8 inch needle (for ELIGARD 1 month, ELIGARD 3 month and ELIGARD 4 month) or a 18-gauge 5/8-inch needle (for ELIGARD 6 month), a silica desiccant pouch to control moisture uptake, and package insert for constitution and administration procedures. Each syringe is

individually packaged. Syringe B, made of cyclic olefin copolymer and sealed with a chlorobutyl closure, contains aseptically filled, lyophilized leuprorelin acetate. Syringe A, constructed of polypropylene and sealed with a polypropylene or polyethylene cap, contains the Atrigel® Delivery System.

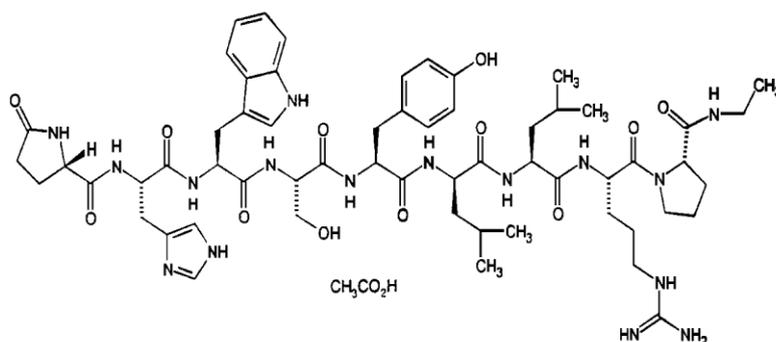
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Leuprorelin acetate is a white to near white powder, freely soluble in water and glacial acetic acid.

### Chemical structure



**Chemical name:** 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)

### CAS number

74381-53-6

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

## 8 SPONSOR

Mundipharma Pty Limited

ABN 87 081 322 509

88 Phillip Street

SYDNEY NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

## **9 DATE OF FIRST APPROVAL**

26 November 2003

## **10 DATE OF REVISION**

6 September 2018

### **SUMMARY TABLE OF CHANGES**

<b>Section Changed</b>	<b>Summary of new information</b>
<b>8</b>	New sponsor and address updated
<b>2, 3</b>	Minor editorial changes
<b>4.4</b>	Safety change: addition of precaution
<b>4.8</b>	Safety change: addition of adverse effect

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ORBIS RA-0191