AUSTRALIAN PI – LUCRIN DEPOT® AND LUCRIN DEPOT® PAEDIATRIC

(LEUPRORELIN ACETATE)

PREFILLED DUAL-CHAMBER SYRINGE (PDS) INJECTION

1 NAME OF THE MEDICINE

Leuprorelin acetate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LUCRIN Depot 1-Month 7.5 mg PDS Injection: each prefilled dual chamber syringe contains 7.5 mg leuprorelin acetate in the front chamber and 1 mL of diluent in the rear chamber.

LUCRIN Depot 3-Month 22.5 mg PDS Injection: each prefilled dual chamber syringe contains 22.5 mg leuprorelin acetate in the front chamber and 1.5 mL of diluent in the rear chamber.

LUCRIN Depot 4-Month 30 mg PDS Injection: each prefilled dual chamber syringe contains 30 mg leuprorelin acetate in the front chamber and 1.5 mL of diluent in the rear chamber.

LUCRIN Depot 6-Month 45 mg PDS Injection: each prefilled dual chamber syringe contains 45 mg leuprorelin acetate in the front chamber and 1.5 mL of diluent in the rear chamber.

LUCRIN Depot Paediatric 30 mg PDS Injection: each prefilled dual chamber syringe contains 30 mg leuprorelin acetate in the front chamber and 1.5 mL of diluent in the rear chamber.

For the full list of excipients, see Section **6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Prefilled dual chamber syringe consisting of powder for injection and diluent.

Powder for injection

White lyophilised powder once reconstituted becomes a milky suspension.

Diluent

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LUCRIN Depot PDS injection is indicated for:

- The palliative treatment of metastatic or locally advanced prostate cancer

LUCRIN Depot Paediatric 3-Month 30mg PDS injection is indicated for:

- The treatment of children with central precocious puberty (CPP).

4.2 Dose and method of administration

Overall treatment with LUCRIN must be done under the supervision of a physician; however, administration of the drug product may be done by a healthcare professional experienced in the administration of intramuscular injections.

LUCRIN Depot PDS Injections are to be used as an intramuscular injection.

There are separate presentations for adult (LUCRIN Depot PDS Injection) and paediatric patients (LUCRIN Depot Paediatric PDS Injection). These presentations should not be replaced and/or substituted for another.

LUCRIN Depot PDS Injection
Prostate Cancer

Serum testosterone concentrations may rise if a dose is omitted or delayed and waning of effect was observed in 3% of patients at week 24, just prior to repeating the injection. It is recommended that testosterone levels are checked in patients, particularly those whose prostate specific antigen (PSA) rises towards the end of the treatment interval.

LUCRIN Depot 1-Month 7.5 mg, 3-Month 22.5 mg, 4-Month 30 mg and 6-Month 45 mg PDS Injections

<u>LUCRIN Depot 1-Month 7.5 mg PDS Injection:</u>

The recommended dose of LUCRIN Depot 1-Month 7.5 mg PDS Injection administration is one injection every 4 weeks. Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics. Incorporated in a depot formulation, the lyophilised microspheres must be reconstituted and should be administered every 4 weeks as a single intramuscular injection.

LUCRIN Depot 3-Month 22.5 mg PDS Injection:

The recommended dose of LUCRIN Depot 3-Month 22.5 mg PDS Injection administration is one injection every 12 weeks. Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics. Incorporated in a depot formulation, the lyophilised microspheres must be reconstituted and should be administered every 12 weeks as a single intramuscular injection.

LUCRIN Depot 4-Month 30 mg PDS Injection:

The recommended dose of LUCRIN Depot 4-Month 30 mg PDS Injection administration is one injection every 16 weeks. Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics. Incorporated in a depot formulation, the lyophilised microspheres must be reconstituted and should be administered every 16 weeks as a single intramuscular injection.

LUCRIN Depot 6-Month 45 mg PDS Injection:

The recommended dose of LUCRIN Depot 6-Month 45 mg PDS Injection administration is one injection every 24 weeks. Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics. Incorporated in a depot formulation, the lyophilised microspheres must be reconstituted and should be administered every 24 weeks as a single intramuscular injection.

LUCRIN Depot Paediatric 3-month 30mg PDS Injection

Central Precocious Puberty

LUCRIN Depot Paediatric 30 mg PDS Injection must only be prescribed after initial assessment by a paediatric endocrinologist, who is experienced in the diagnosis and management of CPP and with the ongoing supervision of such a specialist.

LUCRIN Depot Paediatric 30 mg PDS Injection should be administered once every three months (12 weeks) as a single intramuscular injection. The goal of therapy is to suppress pituitary gonadotropins and peripheral sex steroids, and to arrest progression of secondary sexual characteristics. Hormonal and clinical parameters should be monitored during treatment, for instance at month 2-3, month 6 and further as judged clinically appropriate, to ensure adequate suppression. In case of inadequate suppression, treatment with LUCRIN should be discontinued, and other treatment options for CPP should be considered.

Do not use partial syringes or a combination of syringes to achieve a particular dose.

LUCRIN Depot Paediatric 30 mg PDS Injection treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician. The recommended age at which therapy for CPP should be ceased is at 11 or 12 years of age, for girls and boys respectively.

LUCRIN Depot Paediatric 30 mg PDS Injection must not be injected intra-arterially or intravenously. It is to be used as an intramuscular injection.

Method of administration

For optimal performance of the prefilled dual-chamber syringe (PDS) read and follow the following instructions:

1. To prepare for injection screw the white plunger into the end stopper until the stopper begins to turn.
2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6-8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
3. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) with the diluent thoroughly to form a uniform suspension by gently swirling the syringe. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.
4. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
5. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
6. Inject the entire contents of the syringe intramuscularly at the time of the reconstitution. The suspension settles very quickly following reconstitution; therefore, LUCRIN Depot PDS Injections should be mixed and used immediately. Re-shake the suspension if settling occurs.

NOTE: Aspirated blood would be visible just below the luer lock connection if the blood vessel is accidentally penetrated. If present, blood can be seen through the transparent hub of the needle.

Although the solution has been shown to be stable for 24 hours following reconstitution, the suspension should be discarded if not used immediately, as the product does not contain a preservative.

As with other drugs administered by injection, the injection site should be varied periodically.

LUCRIN Depot PDS Injections contain no antimicrobial agent. LUCRIN Depot PDS Injections are for single use in one patient only. Discard any residue.

4.3 Contraindications

LUCRIN Depot and LUCRIN Depot Paediatric PDS injections are contraindicated in patients with known hypersensitivity to GnRH, GnRH agonists, leuprorelin acetate or similar nonapeptides or any of the excipients. There have been reports of anaphylactic reactions to GnRH agonists (including the monthly formulation of leuprorelin). Isolated cases of anaphylaxis have been reported with the monthly formulation of LUCRIN Depot 1-Month 7.5mg PDS Injection.

Although not expected to be relevant to the approved indications, LUCRIN Depot and LUCRIN Depot Paediatric 30mg PDS Injections are contraindicated when the patient is pregnant or may become pregnant due to its embryotoxic effects (See Section **4.6 Fertility, Pregnancy and Lactation**).

Although not expected to be relevant to the approved indications, LUCRIN Depot and LUCRIN Depot Paediatric PDS Injections should not be administered to a nursing mother, as it is not known whether leuprorelin acetate is excreted into human milk. (See Section **4.6 Fertility, Pregnancy and Lactation**).

4.4 Special warnings and precautions for use

All populations

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed (See Section **5.1 Pharmacodynamic properties**).

Worsening of pre-existing signs and symptoms during the first weeks of treatment may occur. Worsening of symptoms may contribute to paralysis with or without fatal complications.

Bone mineral density

Bone mineral density (BMD) changes can occur during any hypo-estrogenic state. Bone mineral density loss may be reversible after withdrawal of leuprorelin acetate.

BMD may decrease during gonadotropin releasing hormone (GnRH) therapy in children with CPP. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Convulsions

Postmarketing reports of convulsions have been observed in patients on leuprorelin acetate therapy. 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.

Depression and Mood Changes

Depression has been reported in adults who have used leuprorelin for other indications. In children, emotional lability and tearfulness have been reported (see Section **4.8 Adverse effects (Undesirable effects)**).

Delayed Hypersensitivity Reactions

Delayed hypersensitivity reactions including the severe cutaneous adverse reactions (SCAR) of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been very rarely reported postmarketing in association with leuprorelin acetate therapy (see Section **4.8 Adverse effects (Undesirable effects)**). Discontinue future leuprorelin acetate therapy at first signs or symptoms of a delayed hypersensitivity reaction, and treat patients according to current clinical practice.

Men

Flare effect

Initially, LUCRIN Depot PDS injections, like other luteinising hormone-releasing hormone (LH-RH) agonists, cause increases in serum levels of testosterone to approximately 50% above baseline during the first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer may occasionally develop during the first few weeks of LUCRIN Depot Injection treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Initiating therapy with a non-steroidal anti-androgen at the same time as leuprorelin 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).

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

Castration resistant prostate cancer

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

Metabolic changes

The use of androgen deprivation therapy, including GnRH agonists, may be associated with an increased risk of metabolic changes such as hyperglycaemia, diabetes, hyperlipidaemia, and non-alcoholic fatty liver disease (NAFLD). Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Patients at increased risk should be monitored for the signs and symptoms of metabolic syndrome including lipids, blood glucose and-or glycosylated haemoglobin (HbA1c), and managed according to current clinical practice.

Cardiovascular diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with the 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 the development of cardiovascular disease and be managed according to current clinical practice.

Effect on QT/QTc 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 physicians should assess the benefit risk ratio including the potential for *Torsade de pointes* prior to initiating leuprorelin acetate.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of leuprorelin acetate 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, procainamide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

Paediatric population

Central Precocious Puberty

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. In a majority of these 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 sometimes cardiovascular collapse. Immediate medical attention has been required.

Pseudotumor cerebri / idiopathic intracranial hypertension

Pseudotumor cerebri (PTC) / idiopathic intracranial hypertension has been reported in paediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of PTC, including headache, papilloedema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. Refer the patient to an ophthalmologist to confirm the presence of papilloedema. If PTC is confirmed, treat the patient in accordance with established treatment guidelines and permanently discontinue use of leuprorelin acetate.

Use in the elderly

No data available.

Paediatric use

Safety and effectiveness in children have not been established in LUCRIN Depot PDS injection.

LUCRIN Depot Paediatric 3-month 30mg PDS Injection

Safety and efficacy in paediatric patients below the age of 2 years have not been established. The use of LUCRIN Depot Paediatric 30 mg PDS Injection in children under 2 years is not recommended.

Noncompliance with drug regimen or inadequate dosing may result in inadequate control of the pubertal process with gonadotropins and/or sex steroids increasing above prepubertal levels.

CPP is defined as early onset of secondary sexual characteristics (generally earlier than 8 years of age in girls and 9 years of age in boys) associated with pubertal pituitary gonadotropin activation. It may show a significantly advanced bone age that can result in diminished adult height.

Prior to initiation of treatment, a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of LH (basal or stimulated with a GnRH analogue), sex steroids, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumour), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumours), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumour), and adrenal steroid measurements to exclude congenital adrenal hyperplasia.

Effects on laboratory tests

LUCRIN Depot PDS injection

Prostate cancer

Response to leuprorelin acetate therapy may be monitored by measuring serum levels of testosterone, as well as PSA and acid phosphatase. In the majority of non-orchiectomised 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. Due to the suppression of the pituitary-gonadal system by LUCRIN Depot PDS Injections, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUCRIN Depot PDS Injections may be affected.

Serum testosterone levels should be checked periodically in order to assure appropriate suppression, since not all patients achieved testosterone levels below 50 ng/dL and some escaped suppression prior to the end of the 24-week treatment period. In addition, PSA levels should be monitored to identify potential disease progression.

LUCRIN Depot Paediatric 30mg PDS Injection

Central Precocious Puberty

Response to LUCRIN Depot Paediatric 30 mg Injection should be monitored with a GnRH stimulation test, basal LH or serum concentration of sex steroid levels at months 2-3, month 6 and further as judged clinically appropriate, to ensure adequate suppression. Additionally, height (for calculation of growth rate) and bone age should be assessed every 6 to 12 months.

Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

4.5 Interactions with other medicines and other forms of interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUCRIN Depot and LUCRIN Depot Paediatric PDS Injections. However, because leuprorelin acetate is a peptide that is primarily degraded by peptidase and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

See Section **4.4 Special Warnings and Precautions for use-Effect on QT/QTc Interval.**

4.6 Fertility, pregnancy and lactation

Effects on fertility

Clinical and pharmacological studies in adults with leuprorelin 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.

In a clinical study of the 1-month formulation, data to assess reproductive function was collected in a post-study survey of 20 girls who reached adulthood (ages 18-26): menstrual cycles were reported to be normal in 80% of women; 12 pregnancies were reported for a total of 7 of the 20 subjects, including multiple pregnancies for 4 subjects. There are no data in humans relating to male fertility following treatment with leuprorelin acetate.

Following subcutaneous administration of LUCRIN Depot PDS Injection to male and female rats before mating there was atrophy of the reproductive organs and suppression of reproductive performance. Cessation of oestrous cycling was seen in female rats at 2.4 mg/kg/month and reduced fertility was seen in male rats at ≥ 0.8 mg/kg/month. A no effect dose level was not established. These effects were reversed after a long treatment-free period.

Use in pregnancy (Category D)

LUCRIN Depot and LUCRIN Depot Paediatric 30mg PDS Injections are contraindicated in patients who are or may become pregnant while receiving the drug (see Section **4.3 Contraindications**).

Safe use of leuprorelin acetate in pregnancy has not been established in clinical studies. Before starting and during treatment with leuprorelin acetate, it is advisable to establish whether the patient is pregnant. Leuprorelin acetate is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used.

When LUCRIN Depot Paediatric 30 mg PDS Injection was administered subcutaneously to groups of rabbits as one time dosing on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/1900 to 1/19 of the human paediatric dose), it produced a dose-related increase in major foetal abnormalities. Similar studies in rats failed to demonstrate an increase in foetal malformations. There was increased foetal mortality and decreased foetal weights with the two higher doses of LUCRIN Depot Paediatric 30 mg PDS Injection in rabbits and with the highest dose in rats. No foetal malformations but increase in foetal resorptions and mortality were observed in rats and rabbits when the daily injection formulation of leuprorelin acetate was dosed subcutaneously once daily at lower doses (0.1-1 mcg/kg/day in rabbit; 10 mcg/kg/day in rat) during the period of organogenesis. The effects on foetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

Use in lactation

Although not relevant to the approved indication, LUCRIN Depot and LUCRIN Depot Paediatric PDS Injections should not be administered to a nursing mother, as it is not known whether leuprorelin acetate is excreted into human milk. (See Section **4.3 Contraindications**).

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

LUCRIN Depot PDS Injection

Side effects seen with LUCRIN Depot PDS Injections are due to specific pharmacological action; namely, increases and decreases in certain hormone levels.

Prostate cancer

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 of treatment.

'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 leuprorelin 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 leuprorelin acetate therapy with whether this will produce a withdrawal 'flare'.

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

The 4-month formulation of LUCRIN Depot 30 mg PDS Injection, was utilised in clinical trials that studied the drug in 49 non-orchiectomised prostate cancer patients for 32 weeks or longer and in 24 orchiectomised prostate cancer patients for 20 weeks.

In the majority of non-orchiectomised patients, testosterone levels increased 50% or more above baseline during the first week of treatment with LUCRIN Depot PDS Injection, declining thereafter to baseline levels or below by the end of the second week of treatment. Therefore, potential exacerbations of signs and symptoms during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or haematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms.

One open label, multicentre study was conducted with LUCRIN Depot 45 mg PDS Injection for 6–month administration in 151 prostate cancer patients. Patients were treated for 48 weeks, with 139/151 receiving two injections 24 weeks apart.

In a clinical trial of LUCRIN Depot 7.5 mg PDS Injection and in two clinical trials with LUCRIN Depot 3 Month 22.5 mg PDS Injection and the above-mentioned clinical trials with LUCRIN Depot 4-Month 30 mg PDS Injection and LUCRIN Depot 6-Month 45 mg PDS Injection, reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

Table 1: Adverse Drug Reactions in ≥ 5% Patients LUCRIN Depot for 7.5 mg 1 Month, 22.5 mg 3 Month, 30 mg 4 Month and 45 mg 6 Month

	LUCRIN Depot 7.5 mg 1 Month N = 56 (%)	LUCRIN Depot 22.5 mg 3 Month N = 94 (%)	LUCRIN Depot 30 mg 4 Month N = 49 (%) Study 013 Non-orchiectomised	LUCRIN Depot 30 mg 4 Month N = 24 (%) Study 012 Orchiectomised	LUCRIN Depot 45 mg 6 Month N = 151 (%) Study Treatment related
Body as a Whole					
Asthenia	3 (5.4)	7 (7.4)	6 (12.2)	1 (4.2)	
Flu Syndrome			6 (12.2)	0	
General Pain	4 (7.1)	25 (26.6)	16 (32.7)	1 (4.2)	
Headache		6 (6.4)	5 (10.2)	1 (4.2)	
Injection Site Reaction		13 (13.8)	4 (8.2)	9 (37.5)	
Injection Site Pain					15 (9.9)
Fatigue*					15 (9.9)
Cardiovascular System					
Peripheral Oedema	7 (12.5)				
Digestive System					
Nausea / Vomiting	3 (5.4)				
Constipation		6 (6.64)			
GI Disorders		15 (16.0)	5 (10.2)	3 (12.5)	
Nausea		6 (6.64)			
Metabolic and Nutritional Disorders					
Dehydration			4 (8.2)	0	
Oedema			4 (8.2)	5 (20.8)	
Endocrine system					
Decreased Testicular Size*	3 (5.4)				
Hot Flushes / Sweats*	33 (58.9)	55 (58.5)	23 (46.9)	2 (8.3)	87 (57.6)

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	LUCRIN Depot 7.5 mg 1 Month N = 56 (%)	LUCRIN Depot 22.5 mg 3 Month N = 94 (%)	LUCRIN Depot 30 mg 4 Month N = 49 (%) Study 013 Non-orchiectomised	LUCRIN Depot 30 mg 4 Month N = 24 (%) Study 012 Orchiectomised	LUCRIN Depot 45 mg 6 Month N = 151 (%) Study Treatment related
Impotence*	3 (5.4)				
Central/Peripheral Nervous System					
Dizziness/Vertigo		6 (6.4)	3 (6.1)	2 (8.3)	
Insomnia / Somnolence		8 (8.5)			
Neuromuscular Disorders		9 (9.6)	3 (6.1)	1 (4.2)	
Paraesthesia			4 (8.2)	1 (4.2)	
Respiratory System					
Dyspnoea	3 (5.4)				
Respiratory Disorders		6 (6.4)	4 (8.2)	1 (4.2)	
Musculoskeletal System					
Arthralgia		11 (11.7)			
Joint Disorders			8 (16.3)	1 (4.2)	
Musculoskeletal Pain / Myalgia			4 (8.2)	0	
Skin and Appendages					
Skin Reaction		8 (8.5)	6 (12.2)	0	
Urogenital System					
Urinary Disorders		14 (14.9)	5 (10.2)	4 (16.7)	
Testicular Atrophy*		19 (20.2)			
* Physiological effect of decreased testosterone					

Laboratory Abnormalities

LUCRIN Depot 1-Month 7.5 mg PDS Injection and LUCRIN Depot 3-Month 22.5mg PDS Injection

Abnormalities of certain parameters were observed but are difficult to assess in this population. The following were recorded in 5% or more of patients: Increased urea nitrogen, hyperglycaemia, hyperlipidaemia (total cholesterol, LDL-cholesterol, triglycerides), hyperphosphataemia, abnormal liver function tests, increased prothrombin time (PT), increased partial thromboplastin time (PTT). Additional laboratory abnormalities reported were decreased platelets, decreased potassium and increased WBC.

LUCRIN Depot 4-Month 30 mg PDS Injection

In 5% or more of patients who took part in the LUCRIN Depot 4-Month 30mg PDS Injection study, the following abnormalities were observed: decreased bicarbonate, decreased haemoglobin/haematocrit/RBC, hyperlipidaemia (total cholesterol, LDL-cholesterol, triglycerides), decreased HDL-cholesterol, eosinophilia, increased glucose, increased liver function tests (ALT, AST, GGTP, LDH), increased phosphorus. Additional laboratory abnormalities were reported: Increased BUN and PT, leucopenia, thrombocytopenia, uric aciduria.

LUCRIN Depot 6-Month 45mg PDS Injection

Abnormalities of certain parameters were observed, but their relationship to drug treatment is difficult to assess in this population. The following abnormalities were recorded in ≥ 5% of patients: decreased haemoglobin, decreased haematocrit, decreased red blood cells, increased eosinophils, increased AST, increased GGT, increased BUN, increased phosphorus, increased creatinine, increased glucose, increased LDL-cholesterol, increased total cholesterol, increased triglycerides, decreased HDL-cholesterol, and decreased eGFR. Additional laboratory abnormalities reported were increased ALT, increased LDH.

In these same clinical trials, the following adverse reactions were reported in less than 5% of the patients on LUCRIN Depot PDS Injections.

Body as a Whole	-	enlarged abdomen, fever, chills, weight gain, hypothermia, abscess[1], accidental injury[1], allergic reaction[1], cyst[1], generalised oedema[1], hernia[1], neck pain[1,2], neoplasm[1], asthenia[2], feeling hot*[2], injection site discomfort[2], injection site erythema[2], injection site induration[2], injection site nodule[2], injection site swelling[2], injection site warmth[2], oedema peripheral[2], pain[2], pitting oedema[2], injection site cellulitis[2], sinusitis[2], metastases to bone[2].
Cardiovascular System	-	cardiac arrhythmia, bradycardia, heart failure, angina pectoris, hypertension, hypotension, varicose vein, migraine, postural hypotension, atrial fibrillation[1], deep thrombophlebitis[1], tachycardia[2], mitral valve incompetence[2], tricuspid valve incompetence[2].
Digestive System	-	anorexia, diarrhoea, duodenal ulcer, increased appetite, thirst/dry mouth, dyspepsia, rectal disorder, eructation[1], gastrointestinal haemorrhage[1], gingivitis[1], gum haemorrhage[1], hepatomegaly[1], intestinal obstruction[1], periodontal abscess[1], abdominal pain

		upper[2], colonic pseudo-obstruction[2], constipation[2], flatulence[2], haematochezia[2], retching[2], nausea[2].
Musculoskeletal System	-	bone pain, myalgia, leg cramps[1], pathological fracture[1], ptosis[1], arthralgia[2], rib fracture[2], bursitis[2], joint stiffness[2], muscle fatigue[2], muscle spasm[2], osteoarthritis[2], pain in extremity[2].
Central/Peripheral Nervous System	-	paraesthesia, anxiety, delusions, depression, hypaesthesia, decreased libido*, nervousness, hyperkinesia, ataxia, hypertonia, abnormal thinking[1], amnesia[1], convulsion[1], dementia[1], confusion[1], insomnia/sleep disorders[1, 2], neuromuscular disorders[1], neuropathy[1], paralysis[1], depressed mood[2], loss of libido[2], dizziness[2], headache[2], lethargy[2], memory impairment[2].
Respiratory System	-	haemoptysis, epistaxis, pharyngitis, pleural effusion, pneumonia, increased cough, rhinitis, hiccup[1], voice alteration[1], asthma[1], bronchitis[1], dyspnoea[2], dyspnoea exertional[2].
Skin and Appendages	-	dermatitis, hair growth, dry skin, macropapular rash, pruritus, skin discolouration, actinic keratosis[2], cold sweat[2], erythema[2], hyperhidrosis[2], night sweats[2], rash[2], rash pruritic[2].
Urogenital System	-	dysuria, frequency/urgency/impaired, haematuria, testicular pain, gynaecomastia, impotence, penis disorders, testis disorders, nocturia, urinary incontinence[1, 2], testicular atrophy[1, 2], bladder carcinoma[1], epididymitis[1], prostate disorder[1, 2], bladder spasm[2], hydronephrosis[2], hypertonic bladder[2], renal failure[2], urinary hesitation[2], urinary retention[2], urine flow decreased[2], pelvic pain[2].
Haemic and Lymphatic System	-	anaemia, lymphoedema, decreased thromboplastin, leucocytosis, leucopenia, thrombocytopenia, lymphadenopathy[1].
Metabolic and Nutritional Disorders	-	dehydration, oedema, libido decrease, hypercholesteremia, hypokalaemia, healing abnormal[1], hypoxia[1], weight loss[1], central obesity[2], gout[2], hyperkalaemia[2].
Special Senses	-	abnormal vision, amblyopia, dry eyes, tinnitus.
Laboratory	-	increased calcium, increased uric acid, alanine amino transferase (SGPT) increased, aspartate aminotransferase increased (SGOT)[2], blood alkaline phosphatase increased[2], blood glucose increased[2], gamma-glutamyltransferase increased (GGT)[2], heart rate irregular[2,] hepatic enzyme increased[2], liver function test abnormal[2].

Miscellaneous - hard nodule in throat.

* Physiological effect of decreased testosterone.

[1] These adverse reactions were only experienced by patients on LUCRIN Depot 4-Month 30mg PDS Injection study.

[2] These adverse reactions were only experienced by patients on LUCRIN Depot 45mg PDS Injection study.

LUCRIN Depot Paediatric 30mg PDS Injection

Central Precocious Puberty

Note: To provide a complete safety profile of leuprorelin acetate in the CPP population, adverse events for all doses studied in patients with CPP are outlined below. However, the only dosage for the treatment of CPP currently available in Australia is the 30 mg 3-month formulation.

The most common adverse reactions with GnRH agonists including LUCRIN Depot Paediatric 30 mg PDS Injection for 3-month administration are injection site reactions/pain including abscess, general pain, headache, emotional lability and hot flushes/sweating.

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug (hormonal flare effect). Therefore, an increase in clinical signs and symptoms of puberty may be observed (see Section **4.4 Special Warnings and precautions for use**).

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Table 2: Percentage of Patients with Treatment-Emergent Adverse Reactions Occurring in ≥ 2 Paediatric Patients Receiving LUCRIN Depot Paediatric 7.5 mg, 11.25 mg or 15 mg PDS Injection for 1 Month Administration

	Number of Patients (N = 421)	
	N	%
Body as a Whole		
Injection Site Reactions Including Abscess*	37	(9)
General Pain	12	(3)
Headache	11	(3)
Cardiovascular System		
Vasodilation	9	(2)

	Number of Patients (N = 421)	
	N	%
Integumentary System (Skin and Appendages)		
Acne/Seborrhoea	13	(3)
Rash Including Erythema Multiforme	12	(3)
Nervous System		
Emotional Lability	19	(5)
Urogenital System		
Vaginitis/Vaginal Bleeding/Vaginal Discharge	13	(3)
* Most events were mild or moderate in severity.		

Less Common Adverse Reactions with 1-Month Formulations

The following treatment-emergent adverse reactions were reported in less than 2% of the patients and are listed below by body system:

Body as a Whole: aggravation of pre-existing tumour and decreased vision, allergic reaction, body odour, fever, flu syndrome, hypertrophy, infection.

Cardiovascular System: bradycardia, hypertension, peripheral vascular disorder, syncope.

Digestive System: constipation, dyspepsia, dysphagia, gingivitis, increased appetite, nausea/vomiting.

Endocrine System: accelerated sexual maturity, feminisation, goitre.

Haemic and Lymphatic System: purpura.

Metabolic and Nutritional Disorders: growth retarded, peripheral oedema, weight gain.

Musculoskeletal System: arthralgia, joint disorder, myalgia, myopathy.

Nervous System: depression, hyperkinesia, nervousness, somnolence.

Respiratory System: asthma, epistaxis, pharyngitis, rhinitis, sinusitis.

Integumentary System (Skin and Appendages): alopecia, hair disorder, hirsutism, leukoderma, nail disorder, skin hypertrophy.

Urogenital System: cervix disorder/neoplasm, dysmenorrhoea, gynecomastia/breast disorders, menstrual disorders, urinary incontinence.

Laboratory: The following laboratory events were reported as adverse reactions: antinuclear antibody present and increased sedimentation rate.

Table 3: Percentage of Patients with Treatment-Emergent Adverse Reactions Occurring in ≥2 Paediatric Patients Receiving LUCRIN Depot Paediatric 11.25 mg or 30 mg PDS Injection for 3 Month Administration

	11.25 mg every 3 Months N=42		30 mg every 3 Months N=42	
	N	%	N	%
Injection site pain	8	(19)	9	(21)
Weight increased	3	(7)	3	(7)
Headache	1	(2)	3	(7)
Mood altered	2	(5)	2	(5)
Injection site swelling	1	(2)	1	(2)

Less Common Adverse Reactions with 3-Month Formulations

The following treatment-emergent adverse reactions were reported in one patient and are listed below by system organ class:

Gastrointestinal Disorders: abdominal pain, nausea.

General Disorders and Administration Site Conditions: asthenia, gait disturbance, injection site abscess sterile, injection site hematoma, injection site induration, injection site warmth, irritability.

Metabolic and Nutritional Disorders: decreased appetite, obesity.

Musculoskeletal and Connective Tissue Disorders: musculoskeletal pain, pain in extremity.

Nervous System Disorders: crying, dizziness.

Psychiatric Disorders: tearfulness.

Respiratory, Thoracic and Mediastinal Disorders: cough.

Skin and Subcutaneous Tissue Disorders: hyperhidrosis.

Vascular Disorders: pallor.

In clinical trials and postmarketing surveillance, the following adverse events have been observed with formulations of leuprorelin acetate. As leuprorelin has multiple indications and therefore patient populations, some of these adverse events may not be applicable to every patient. For a majority of these adverse events, a cause and effect relationship has not been established.

Body as a Whole: infection/inflammation, abdomen enlarged, asthenia, chills, fever, general pain, headache, swelling (temporal bone), jaundice.

Cardiovascular System: congestive heart failure, ECG changes/ischaemia, myocardial infarction, murmur, pulmonary emboli, sudden cardiac death, transient ischaemic attack/stroke, chest pain, angina, bradycardia, cardiac arrhythmia, tachycardia.

Digestive System: abdominal pain, abdominal distention, constipation, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, gastrointestinal disorder, peptic ulcer, rectal polyps, diarrhoea, dry mouth, duodenal ulcer, increased appetite, liver function tests abnormal, nausea, thirst, vomiting.

Endocrine: diabetes, thyroid enlargement, pituitary apoplexy.

Metabolic and Nutritional System: BUN increased, calcium increased, creatinine increased, dehydration, oedema, hyperlipidaemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphatemia, hypoglycaemia, hypoproteinemia, potassium decreased, urea/uric acid increased, bilirubin increased, weight gain.

Hepato-biliary disorder: hepatic dysfunction, serious liver injury, non-alcoholic fatty liver disease.

Haemic and Lymphatic System: anaemia, decreased WBC, PT increased, PTT increased, platelets decreased, increased WBC.

Musculoskeletal System: ankylosing spondylosis, joint pain, pelvic fibrosis, tenosynovitis-like symptoms, joint disorders, myalgia, spinal fracture, paralysis, bone swelling, arthropathy, arthralgia.

Nervous System: anxiety, convulsion, dizziness/light-headiness, headache, hearing disorder, sleep disorders, lethargy, memory disorder, mood swings, nervousness, numbness, peripheral neuropathy, depression, delusion, hypasthenia, hypoaesthesia, insomnia, increased libido, neuromuscular disorders, paraesthesia, syncope/blackouts, cerebrovascular accident, loss of consciousness, neuromyopathy, pseudotumor cerebri/idiopathic intracranial hypertension.

Respiratory System: cough, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion, dyspnoea, epistaxis, haemoptysis, pharyngitis, pleural effusion, interstitial lung disease.

Skin and subcutaneous tissue disorders: hyperhidrosis, alopecia, ecchymosis, erythema multiforme, carcinoma of skin/ear, dry skin, hair loss, pigmentation, skin lesions, dermatitis, hair growth, hard nodule in throat, pruritus, rash, urticaria, itching, photosensitivity reactions, dermatitis bullous, dermatitis exfoliative, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis.

Urogenital System: pollakiuria, bladder spasms, incontinence, penile swelling, prostate pain, urinary obstruction, urinary tract infection, breast pain, breast tenderness, gynaecomastia, haematuria, menstrual disorders including breakthrough and sustained vaginal bleeding, metrorrhagia, penile disorders, testicular atrophy, testicular pain, testicular disorder, testicular size decrease, urinary disorders, urinary frequency, urinary urgency.

Special Senses: ophthalmologic disorders, abnormal vision, amblyopia, blurred vision, visual impairment, dry eyes, hearing disorders, taste disorders, tinnitus.

Vascular disorders: hot flush, lymphoedema, hypertension, hypotension, phlebitis, thrombosis, varicose vein.

Injection site reactions including pain, infection, inflammation, sterile abscess, necrosis, nodule, induration and haematoma have been reported.

There have been very rare reports of suicidal ideation and attempt.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.

Isolated cases of anaphylaxis have been reported.

<u>Changes in bone density</u>

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analogue. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprorelin acetate for at least six months, underwent bone density studies as a result of pain. The leuprorelin-treated group had lower bone density scores than the non-treated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists. Post-marketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression. A definitive cause and effect relationship between the treatment with GnRH agonists and the occurrence of these events has not been established. Monitor for development or worsening of psychiatric symptoms during treatment with leuprorelin acetate.

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. In Australia, healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

In early clinical trials with 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.

In rats, subcutaneous administration of 250 to 500 times the recommended adult human dose expressed on a per bodyweight basis, results in dyspnoea, decreased activity and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with 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 1mg/day dose.

In rats, subcutaneous administration of leuprorelin acetate as a single dose 225 times the recommended human paediatric dose, expressed on a per body weight basis, resulted in dyspnoea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring (GnRH) or luteinising hormone releasing hormone (LH-RH). The analogue possesses greater potency than the natural hormone.

Leuprorelin acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses and is chemically unrelated to the steroids. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprorelin acetate results in suppression of ovarian and testicular steroidogenesis.

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 LH and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males and estrone and estradiol in pre-menopausal females). However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In 93.7% of males, androgens are reduced to castrate or pre-pubertal levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within a month of initiating treatment and are maintained as long as treatment continues.

In prostate cancer, during the course of treatment, testosterone levels should be monitored to ensure there has been adequate suppression, as treatment effects are not always maintained.

Clinical trials

LUCRIN Depot PDS Injection

Prostate Cancer

LUCRIN Depot 1-month 7.5 mg PDS Injection

In an open-label, non-comparative, multicentre clinical study of LUCRIN Depot 1-month 7.5 mg PDS Injection, 56 patients with stage D2 prostatic adenocarcinoma and no prior systemic treatment were enrolled. The objectives were to determine if a 7.5 mg depot formulation of leuprorelin injected once every 4 weeks would reduce and maintain serum testosterone to castrate range (≤50 ng/dL), to evaluate objective clinical response, and to assess the safety of the formulation. During the initial 24 weeks, serum testosterone was measured weekly,

biweekly, or every four weeks and objective tumour response assessments were performed at Weeks 12 and 24. Once the patient completed the initial 24-week treatment phase, treatment continued at the investigator's discretion. Data from the initial 24-week treatment phase are summarised in this section.

In the majority of patients, serum testosterone increased by 50% or more above baseline during the first week of treatment. Serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54) of patients for whom testosterone suppression was achieved (2 patients withdrew prior to onset of suppression) and within 66 days in all 54 patients. Mean serum testosterone suppressed to castrate level by Week 3. The median dosing interval between injections was 28 days. One escape from suppression (2 consecutive testosterone values greater than 50 ng/dL after achieving castrate level) was noted at Week 18, associated with a substantial dosing delay. In this patient, serum testosterone returned to the castrate range at the next monthly measurement. Serum testosterone was minimally above the castrate range on a single occasion for 4 other patients. No clinical significance was attributed to these rises in testosterone.

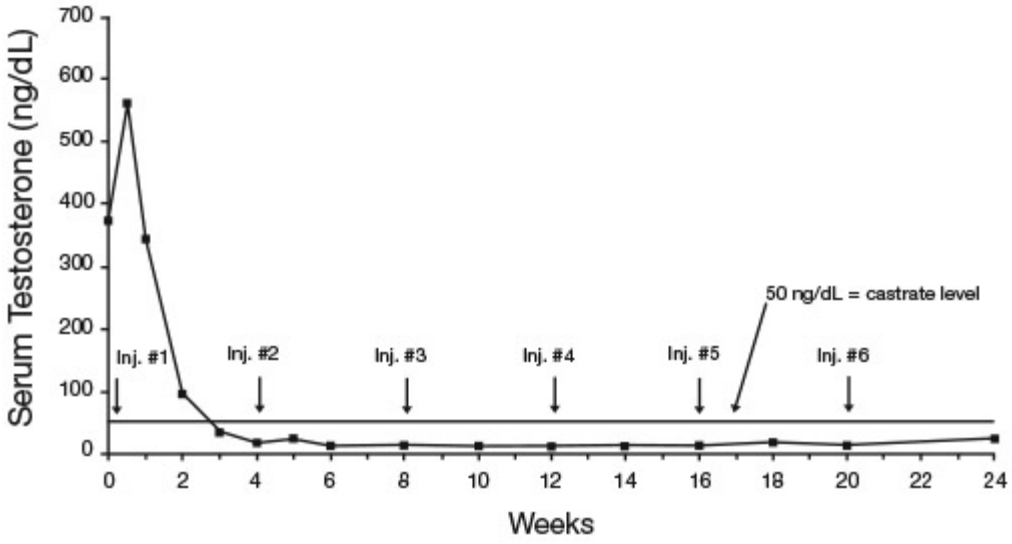


Figure 1. LUCRIN Depot 7.5 mg for 1-Month Administration Mean Serum Testosterone Concentrations

Secondary efficacy endpoints evaluated included objective tumour response, assessed by clinical evaluations of tumour burden (complete response, partial response, objectively stable, and progression), as well as changes in local disease status, assessed by digital rectal examination, and changes in prostatic acid phosphatase (PAP). These evaluations were performed at Weeks 12 and 24. The objective tumour response analysis showed a "no progression" (i.e. complete or partial response, or stable disease) in 77% (40/52) of patients at Week 12, and in 84% (42/50) of patients at Week 24. Local disease improved or remained

stable in all (42) patients evaluated at Week 12 and in 98% (41/42) of patients elevated at Week 24. PAP normalised or decreased at Week 12 and/or 24 in the majority of patients with elevated baseline PAP.

Periodic monitoring of serum testosterone and PSA levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that 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.

LUCRIN Depot 3-Month 22.5 mg PDS Injection

In clinical studies, serum testosterone was suppressed to castrate within 30 days in 87 of 92 (95%) patients and within an additional two weeks in three patients. Two patients did not suppress for 15 and 28 weeks, respectively. Suppression was maintained in all of these patients with the exception of transient minimal testosterone elevations in one of them, and in another an increase in serum testosterone to above the castrate range was recorded during the 12-hour observation period after a subsequent injection. This represents stimulation of gonadotropin secretion.

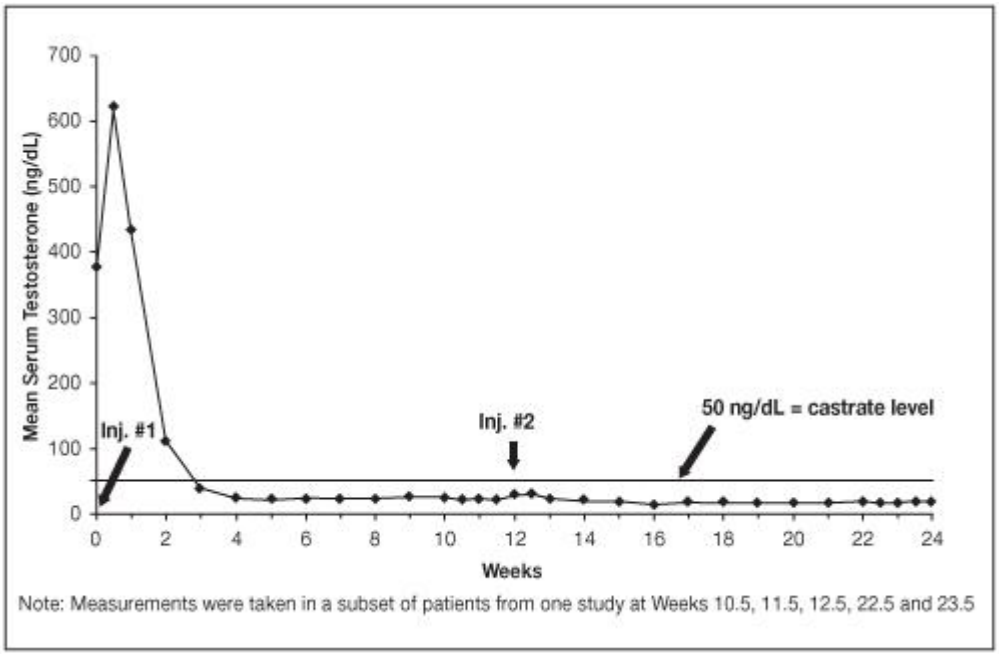


Figure 2. LUCRIN Depot 22.5 mg PDS Injection for 3-Month Administration Mean Serum Testosterone Concentrations

An 85% rate of "no progression" was achieved during the initial 24 weeks of treatment. A decrease from baseline in serum PSA of ≥90% was reported in 71% of the patients and a change to within the normal range (≤3.99 ng/mL) in 63% of the patients.

Periodic monitoring of serum testosterone and PSA levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that 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.

LUCRIN Depot 4-Month 30 mg PDS Injection

In an open-label, noncomparative, multicentre clinical study of LUCRIN Depot 30 mg PDS Injection, 49 patients with stage D2 prostatic adenocarcinoma (with no prior treatment) were enrolled. The objectives were to determine whether a 30 mg depot formulation of leuprorelin injected once every 16 weeks would reduce and maintain serum testosterone levels at castrate levels (≤ 50 ng/dL), and to assess the safety of the formulation. The study was divided into an initial 32-week treatment phase and a long-term treatment phase. Serum testosterone levels were determined biweekly or weekly during the first 32 weeks of treatment. Once the patient completed the initial 32-week treatment period, treatment continued at the investigator's discretion with serum testosterone levels being done every 4 months prior to the injection.

In the majority of patients, testosterone levels increased 50% or more above the baseline during the first week of treatment. Mean serum testosterone subsequently suppressed to castrate levels within 30 days of the first injection in 94% of patients and within 43 days in all 49 patients during the initial 32-week treatment period. The median dosing interval between injections was 112 days. One escape from suppression (two consecutive testosterone values greater than 50 ng/dL after castrate levels achieved) was noted at Week 16. In this patient, serum testosterone increased to above the castrate range following the second depot injection (Week 16) but returned to the castrate level by Week 18. No adverse reactions were associated with this rise in serum testosterone. A second patient had a rise in testosterone at Week 17, then returned to the castrate level by Week 18 and remained there through Week 32. In the long-term treatment phase two patients experienced testosterone elevations, both at Week 48. Testosterone for one patient returned to the castrate range at Week 52, and one patient discontinued the study at Week 48 due to disease progression.

Secondary efficacy endpoints evaluated in the study were the objective tumour response as assessed by clinical evaluations of tumour burden (complete response, partial response,

objectively stable and progression) and evaluations of changes in prostatic involvement and PSA. These evaluations were performed at Weeks 16 and 32 of the treatment phase. The long-term treatment phase monitored PSA at each visit (every 16 weeks). The objective tumour response analysis showed "no progression" (i.e. complete or partial response, or stable disease) in 86% (37/43) of patients at Week 16, and in 77% (37/48) of patients at Week 32. Local disease improved or remained stable in all patients evaluated at Week 16 and/or 32. For patients with elevated baseline PSA, 50% (23/46) had a normal PSA (less than 4.0 ng/mL) at Week 16, and 51% (19/37) had a normal PSA at Week 32.

Periodic monitoring of serum testosterone and PSA levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that 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.

Using historical comparisons, the safety and efficacy of LUCRIN Depot 30 mg PDS Injection appear similar to the other LUCRIN Depot formulations.

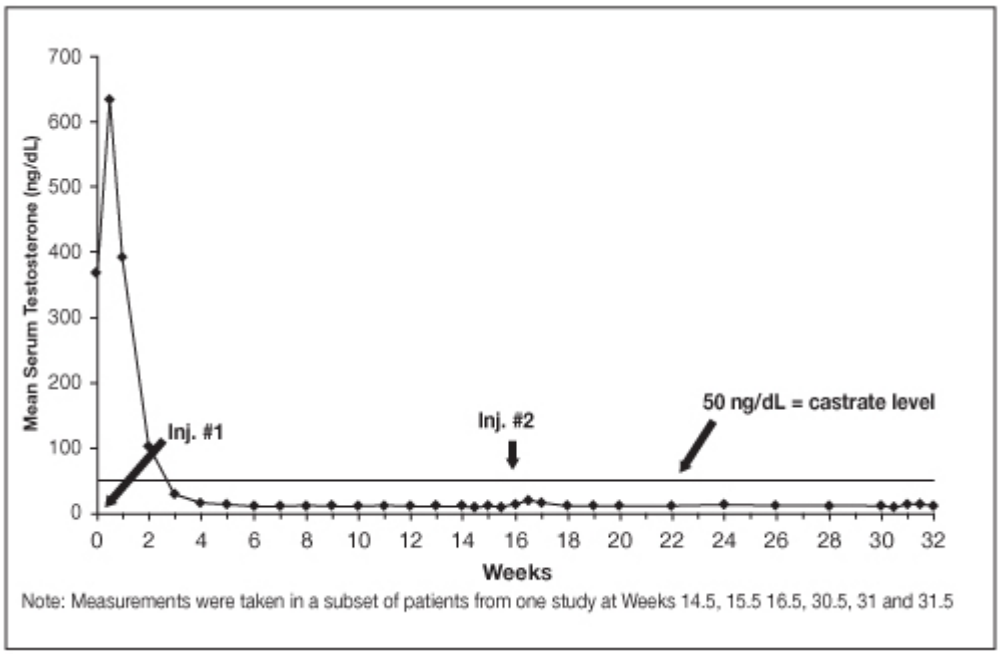


Figure 3. LUCRIN Depot 30 mg PDS Injection for 4-Month Administration Mean Serum Testosterone Concentrations

LUCRIN Depot 6-Month 45 mg PDS Injection

An open-label, non-comparative, multicentre clinical study of LUCRIN Depot 45 mg PDS Injection enrolled 151 patients with prostate cancer. The study drug was administered as two intramuscular injections of LUCRIN Depot 45 mg PDS Injection at 24 week intervals (139/151 received 2 injections), and patients were followed for a total of 48 weeks.

Among 148 patients who had testosterone value at Week 4, serum testosterone was suppressed to castrate levels (< 50 ng/dL) from Week 4 through Week 48 in an estimated 93.4% (two-sided 95% CI: 89.2%, 97.6%) of patients. One patient failed to achieve testosterone suppression by Week 4, and eight patients had escapes from suppression (any testosterone value > 50 ng/dL after castrate levels were achieved). Mean testosterone levels increased to 608 ng/dL from a baseline of 435 ng/dL during the first week of treatment. By Week 4, the mean testosterone concentration had decreased to below castrate levels (16 ng/dL).

Periodic monitoring of serum testosterone levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. Testosterone determinations are dependent on assay methodology and it is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Figure 4 below shows the mean testosterone concentration at various time points.

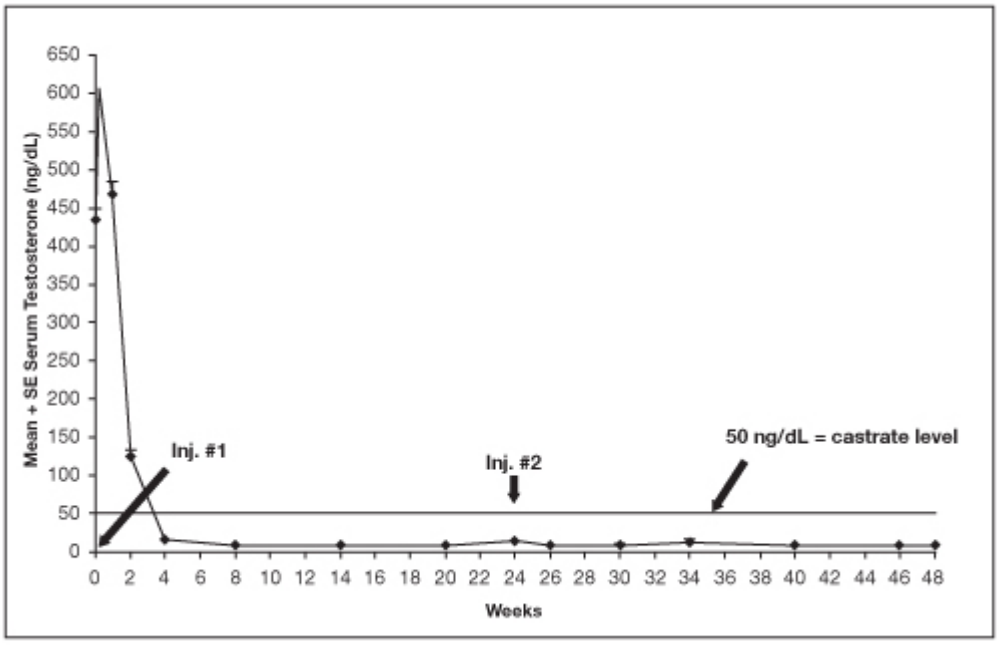


Figure 4. LUCRIN Depot 45 mg PDS injection for 6-Month Administration Serum Testosterone Concentrations (Mean + SE)

Patients at risk of spinal cord compression and urinary tract obstruction were excluded from this study.

LUCRIN Depot Paediatric PDS Injection

Central Precocious puberty

In children with CPP, stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females respectively.

LUCRIN Depot Paediatric PDS Injection 11.25 mg or 30 mg for 3 Month Administration

In a randomised, open-label clinical study (L-CP07-167) of LUCRIN Depot Paediatric 3 month formulations, 84 subjects (76 female, 8 male), with a mean age of 7.8 years (range 1 to 11 years), received the 11.25 mg and 30 mg formulation as a single intramuscular injection every 3 months. Each dose group had an equal number of treatment-naïve patients who had pubertal LH levels and patients previously treated with GnRH therapies who had prepubertal LH levels at the time of study entry. The percentage of subjects with suppression of peak-stimulated LH to < 4.0 mIU/mL, as determined by assessments at months 2, 3 and 6, was 78.6% in the 11.25 mg dose group and 95.2% as shown in Table 4.

Table 4: Suppression of Peak-Stimulated LH from Month 2 through Month 6

	LUCRIN Depot Paediatric 30 mg every 3 Months		
Parameter	Naïve N = 21	Previously Treated [a] N = 21	Total N = 42
Percent with Suppression	90.5	100	95.2
2-sided 95% CI	69.6, 98.8	83.9, 100	83.8, 99.4
[a] Previously treated with GnRHa for at least 6 months prior to enrolment in pivotal Study L-CP07-167			

The mean peak stimulated LH levels for all visits are shown by dose and subgroup (naïve vs. previously treated subjects) in Figure 5.

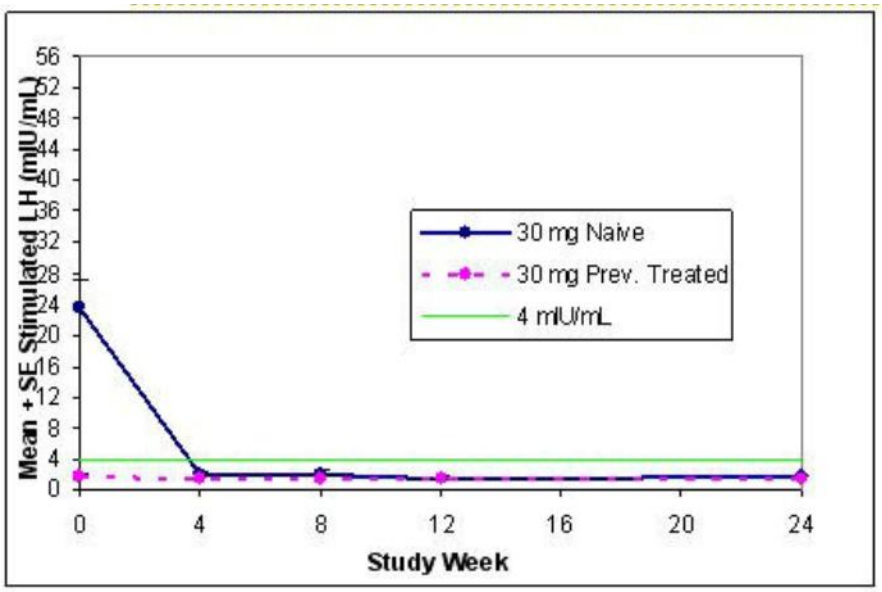


Figure 5. Mean Peak Stimulated LH for LUCRIN Depot Paediatric 3 Month 30 mg PDS Injections

5.2 Pharmacokinetic properties

Leuprorelin acetate is not active when given orally. Intramuscular injection of the depot formulation provides plasma concentrations of leuprorelin acetate over a period of one month with LUCRIN Depot 7.5 mg 1-month PDS Injection, over three months for LUCRIN Depot 22.5 mg 3-Month PDS Injection, over four months for LUCRIN Depot 30 mg 4-Month PDS Injection, over six months for LUCRIN Depot 30 mg 6-Month PDS Injection, and three months for LUCRIN Depot Paediatric 30 mg PDS Injection.

Absorption

A mean peak plasma leuprorelin acetate concentration of 48.9 ng/mL was observed at 4 hours following a single injection of the three-month formulation of LUCRIN Depot 22.5 mg PDS Injection. It then declined to 0.67 ng/mL at 12 weeks. Leuprorelin acetate appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. However, intact leuprorelin and an inactive major metabolite could not be distinguished by the assay that was employed in the study. Detectable levels of leuprorelin acetate were present at all measurement points in all patients. The initial burst, followed by a decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Following a single injection of the four-month formulation of LUCRIN Depot 30 mg PDS Injection in patients, a mean peak plasma leuprorelin concentration of 59.3 ng/mL was

observed at 4 hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks. Leuprorelin appeared to be released at a constant rate following the onset of steady-state levels during the fourth week after dosing, providing steady plasma concentrations throughout the 16-week dosing interval. Again, intact leuprorelin and an inactive major metabolite could not be distinguished by the assay that was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations.

Following a single injection of leuprorelin acetate depot 6-month 45 mg in 26 prostate cancer patients, mean peak plasma leuprorelin concentration of 6.7 ng/mL was observed at 2 hours and the mean concentration then declined to 0.07 ng/mL at 24 weeks. Leuprorelin appeared to be released continuously following the onset of steady-state levels during the third week after dosing providing steady plasma concentrations through the 24-week dosing interval. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations. In this study, mean leuprorelin plasma concentration-time profiles were similar after the first and second dose.

Following a single LUCRIN Depot Paediatric PDS Injection, 30 mg for 3-month administration to children with CPP, the mean peak leuprorelin plasma concentration was 52.5 ng/mL. The concentrations then declined to 0.25 ng/mL at 2 weeks after dosing. Mean leuprorelin plasma concentration remained constant from month 1 to month 3. The mean leuprorelin concentrations 3 months after the first and second injections were similar indicating no accumulation of leuprorelin from repeated administration.

Distribution

The mean steady-state volume 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 and excretion

In healthy male volunteers, a 1mg 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.

Animal studies have shown ^{14}C-labelled leuprorelin was metabolised into smaller peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further metabolised.

Special Populations

The pharmacokinetics of the drug in patients with hepatic and renal impairment have not been determined.

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have been performed with leuprorelin acetate using bacterial and mammalian systems. These studies provided no evidence of a genotoxic potential.

Carcinogenicity

A two-year carcinogenicity study was conducted 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). This study also revealed an increased incidence of pancreatic islet cell adenomas, but their incidence showed a negative trend with dose, suggesting that it may not be drug-related. In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. In short term toxicity studies in mice treated for 3 months with 20-200 mg/kg, hypertrophic and castration cells were found in the anterior pituitary. Neither pituitary nor pancreatic changes were found in cynomolgus monkeys treated for 12 months with 10 mg/kg daily.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LUCRIN Depot 1-month 7.5mg PDS Injection contains leuprorelin acetate (7.5mg), gelatin, polyglactin and mannitol. The accompanying diluent contains carmellose sodium, mannitol, polysorbate 80, water for injections (1mL) and glacial acetic acid to control pH.

LUCRIN Depot 3-Month 22.5 mg PDS Injection contains leuprorelin acetate (22.5mg), polylactic acid and mannitol. The accompanying diluent contains carmellose sodium, mannitol, polysorbate 80, water for injections (1.5mL) and glacial acetic acid to control pH.

LUCRIN Depot 4-Month 30 mg PDS Injection contains leuprorelin acetate (30mg), polylactic acid and mannitol. The accompanying diluent contains carmellose sodium, mannitol, polysorbate 80, water for injections USP (1.5mL) and glacial acetic acid USP to control pH.

LUCRIN Depot 6-Month 45 mg PDS Injection contains leuprorelin acetate (45 mg equivalent to 42.9 mg of leuprorelin), polylactic acid, mannitol and stearic acid. The accompanying

diluent contains carmellose sodium, mannitol, polysorbate 80, water for injections USP (1.5mL) and glacial acetic acid Ph. Eur. to control pH.

LUCRIN Depot Paediatric 30 mg PDS Injection contains leuprorelin acetate (30 mg), polylactic acid and mannitol. The accompanying diluent contains carmellose sodium, mannitol, polysorbate 80, water for injections USP (1.5 mL) and glacial acetic acid USP to control pH.

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

Store below 25°C. Protect from light.

6.5 Nature and contents of container

LUCRIN Depot 1-month 7.5 mg PDS Injection is available as sterile lyophilised microspheres, which, when mixed with diluent, becomes a suspension, intended for administration as a monthly intramuscular injection. Clear, colourless type I glass cartridge with rubber stopper. Front chamber with 7.5 mg powder for solution for injection, rear chamber containing 1mL diluent.

LUCRIN Depot 3-Month 22.5 mg PDS Injection is available as sterile lyophilised microspheres, which, when mixed with diluent, becomes a suspension, for administration as a single intramuscular injection every three months. Clear, colourless type I glass cartridge with rubber stopper. Front chamber with 22.5 mg powder for solution for injection, rear chamber containing 1.5mL diluent.

LUCRIN Depot 4-Month 30 mg PDS Injection is available as sterile lyophilised microspheres, which when mixed with diluent, becomes a suspension which is intended as an intramuscular injection to be given every four months. Clear, colourless type I glass cartridge with rubber stopper. Front chamber with 30 mg powder for solution for injection, rear chamber containing 1.5mL diluent.

LUCRIN Depot 6-Month 45 mg PDS Injection is available as sterile lyophilised microspheres, which when mixed with diluent, becomes a suspension which is intended as an intramuscular injection to be given every six months. Clear, colourless type I glass cartridge with rubber stopper. Front chamber with 45 mg powder for solution for injection, rear chamber containing 1.5mL diluent.

LUCRIN Depot Paediatric 30 mg PDS Injection is available as sterile lyophilised microspheres, which, when mixed with diluent, becomes a suspension, for administration as a single intramuscular injection every three months. Clear, colourless type I glass cartridge with rubber stopper. Front chamber with 30 mg powder for solution for injection, rear chamber containing 1.5mL diluent.

6.6 Special precautions for disposal

Although the suspension has been shown to be stable for 24 hours following reconstitution, it should be discarded if not used immediately.

LUCRIN Depot PDS Injections contain no antimicrobial agent. LUCRIN Depot PDS Injections are for single use in one patient only. Discard any residue.

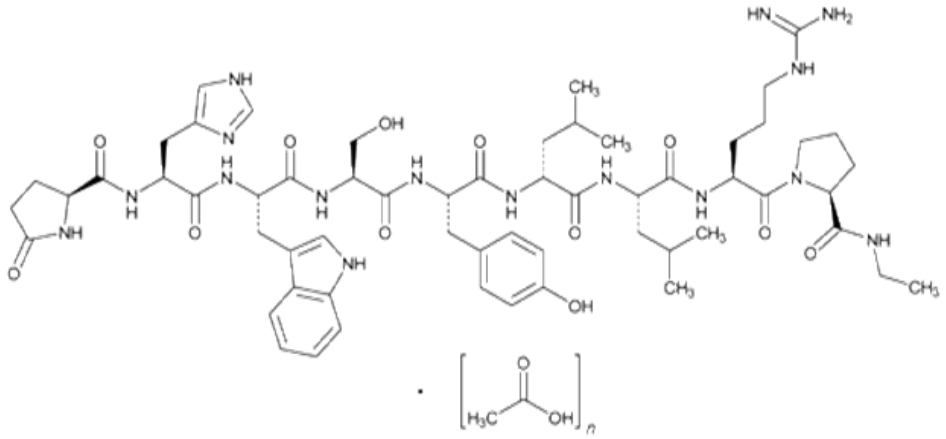
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Leuprorelin acetate is a hygroscopic, white or almost white powder. It has a molecular formula of $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ and a molecular weight of 1269.47. The solubility of leuprorelin acetate in water is more than 75% and less than 0.0001% in ether and hexane.

The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt).

Chemical structure



CAS number

53714-56-0 (leuprorelin free peptide)

74381-53-6 (leuprorelin acetate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
Australia
Tel: 1800 043 460

9 DATE OF FIRST APPROVAL

8 April 2005

LUCRIN Depot 1-month 7.5mg PDS Injection (AUST R 114302)

LUCRIN Depot 3-Month 22.5 mg PDS Injection (AUST R 114303)

LUCRIN Depot 4-Month 30mg PDS Injection (AUST R 114304)

12 May 2015

LUCRIN Depot 6-Month 45 mg PDS Injection (AUST R 222375)

13 October 2014

LUCRIN Depot Paediatric 30 mg PDS Injection (AUST R 218936)

10 DATE OF REVISION

21 February 2025

Version 19

Summary table of changes

Section changed	Summary of new information
Section 4.8	Addition of necrosis to postmarketing section.