PRODUCT INFORMATION

LUCRIN® DEPOT PREFILLED DUAL-CHAMBER SYRINGE (PDS) INJECTION

NAME OF THE MEDICINE

NON-PROPRIETARY NAME
Leuprorelin acetate

Chemical Structure

CAS Number
74381-53-6

DESCRIPTION
Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analogue possesses greater potency than the natural hormone. Leuprorelin acetate acts as an inhibitor of gonadotropin production and is chemically unrelated to the steroids. 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).

Leuprorelin acetate is a hygroscopic, white or almost white powder. It has a molecular formula of C59H84N16O12.C2H4O2 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.

Lucrin Depot 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.

Lucrin Depot 7.5mg PDS Injection contains leuprorelin acetate (7.5mg), gelatin (1.3mg), polyglactin (66.2mg) and mannitol (13.2mg). The accompanying diluent contains carmellose sodium (5mg), mannitol (50mg), polysorbate 80 (1mg), water for injections (1mL) and glacial acetic acid to control pH.

Lucrin Depot 3-Month 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.

Lucrin Depot 3-Month PDS Injection contains leuprorelin acetate (22.5mg), polylactic acid (198.6mg) and mannitol (38.9mg). The accompanying diluent contains carmellose sodium (7.5mg), mannitol (75mg), polysorbate 80 (1.5mg), water for injection (1.5mL) and glacial acetic acid to control pH.
Lucrin Depot 4-Month PDS Injection is available as sterile lyophilised microspheres, which when mixed with diluent, become a suspension which is intended as an intramuscular injection to be given every four months.

Lucrin Depot 4-Month PDS Injection contains leuprorelin acetate (30mg), polylactic acid (264.8mg) and mannitol (51.9mg). The accompanying diluent contains carmellose sodium (7.5mg), mannitol (75mg), polysorbate 80 (1.5mg), water for injections USP (1.5mL) and glacial acetic acid USP to control pH.

**CLINICAL PHARMACOLOGY**

Leuprorelin acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. 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 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 pre-menopausal females). However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH. In males, androgens are reduced to castrate or pre-pubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These decreases occur within a month of initiating treatment and are maintained as long as treatment continues.

**Pharmacokinetics**

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 PDS Injection and over three months for Lucrin Depot 3-Month PDS Injection and over four months for Lucrin Depot 4-Month PDS Injection.

A mean peak plasma leuprorelin concentration of 48.9 ng/mL was observed at 4 hours following a single injection of the three-month formulation of Lucrin Depot 22.5mg 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 30mg Injection in patients, a mean peak plasma leuprorelin concentration of 59.3ng/mL was observed at 4 hours and the mean concentration then declined to 0.30ng/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.

The mean steady-state volume distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27L. In vitro binding to human plasma proteins ranged from 43% to 49%.
In healthy male volunteers, a 1mg bolus of leuprorelin administered intravenously revealed that the mean systemic clearance was 7.6L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

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

**INDICATIONS**

Lucrin Depot 7.5 mg PDS Injection, Lucrin Depot 3-Month PDS Injection, and Lucrin Depot 4-Month PDS Injection are indicated in the palliative treatment of metastatic or locally extensive prostatic cancer (Stage C and D).

**CONTRAINDICATIONS**

Although not relevant to the approved indication, leuprorelin acetate is contraindicated in pregnancy due to its embryotoxic effects. (See PRECAUTIONS – Use in Pregnancy)

Although not relevant to the approved indication, Lucrin Depot PDS Injection should not be administered to a nursing mother, as it is not known whether leuprorelin acetate is excreted into human milk. (See PRECAUTIONS – Use in Lactation)

Lucrin Depot PDS Injection is contraindicated in patients with known hypersensitivity to leuprorelin acetate or similar nonapeptides or any of the excipients. Isolated cases of anaphylaxis have been reported with the monthly formulation of Lucrin Depot 7.5 mg Injection.

**PRECAUTIONS**

Initially, Lucrin Depot PDS injections, like other LH-RH agonists, causes 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 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.

For patients at risk, the physician may consider initiating therapy with daily Lucrin (leuprorelin acetate) injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving GnRH agonists and manage with current practice for treatment of hyperglycaemia or diabetes.

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 development of cardiovascular disease and be managed according to current clinical practice.

**Effect on QT/QTc Interval**

QT-prolongation has been observed during long-term androgen deprivation therapy. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks.
in patients with congenital long QT syndrome, electrolyte abnormalities or congestive heart failure and in patients taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

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.

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

Convolusions
Postmarketing reports of convulsions have been observed in patients on leuprorelin acetate therapy. These included patients in the female and pediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, 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.

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.

Use in Pregnancy (Category D)
Although not relevant to the approved indication, leuprorelin acetate is contraindicated in pregnancy due to its embryotoxic effects. (See CONTRAINDICATIONS)

Use in Lactation
Although not relevant to the approved indication, Lucrin Depot PDS Injection should not be administered to a nursing mother, as it is not known whether leuprorelin acetate is excreted into human milk. (See CONTRAINDICATIONS)

Paediatric Use
Safety and effectiveness in children have not been established

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.

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

No pharmacokinetic-based drug-drug interaction studies have been conducted with Lucrin Depot PDS Injection. However, because leuprolrelin 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.

Effect on Laboratory Tests

Response to leuprolrelin acetate therapy may be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen and acid phosphatase. In the majority of non-orchiectomized 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, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of Lucrin Depot may be affected.

ADVERSE EFFECTS

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

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

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

The 4-month formulation of Lucrin Depot 30mg was utilised in clinical trials that studied the drug in 49 nonorchiectomized prostate cancer patients for 32 weeks or longer and in 24 orchiectomized prostate cancer patients for 20 weeks.

In the majority of nonorchiectomized patients, testosterone levels increased 50% or more above baseline during the first week of treatment with Lucrin Depot, 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 hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.

In a clinical trial of Lucrin Depot 7.5 mg Injection and in two clinical trials with Lucrin Depot 3 Month 22.5 mg Injection and the abovementioned clinical trial with Lucrin Depot 4-Month 30mg 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.

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<tr>
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<th>LUCRIN DEPOT 7.5mg</th>
<th>LUCRIN DEPOT 22.5mg</th>
<th>LUCRIN DEPOT 30mg</th>
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<td>N = 94 (%)</td>
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<td>Dyspnoea</td>
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<td>Nonorchiectomized</td>
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</table>

**Respiratory Disorders**
- LUCRIN DEPOT 7.5mg: 6 (6.4)
- LUCRIN DEPOT 22.5mg: 4 (8.2)
- LUCRIN DEPOT 30mg: 1 (4.2)

**Musculoskeletal System**
- Arthralgia: 11 (11.7)
- Joint Disorders: 8 (16.3)
- Myalgia: 4 (8.2)

**Digestive System**
- GI Disorders: 15 (16.0)
- Skin and Appendages
  - Skin Reaction: 8 (8.5)
- Urogenital System
  - Urinary Disorders: 15 (14.9)
  - Testicular Atrophy*: 19 (20.2)

* Physiological effect of decreased testosterone

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Lucrin Depot 7.5mg and Lucrin Depot 3-Month 22.5mg

Laboratory: 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 30mg

In 5% or more of patients who took part in the Lucrin Depot 4-Month 30mg 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, leukopenia, thrombocytopenia, uricaciduria.

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

- **Body as a Whole**
  - enlarged abdomen, fever, chills, weight gain, hypothermia, abscess4, accidental injury4, allergic reaction4, cyst4, generalised oedema4, hernia4, neck pain4, neoplasm4

- **Cardiovascular System**
  - cardiac arrhythmia, bradycardia, heart failure, angina, hypertension, hypotension, varicose vein,
migraine, postural hypotension, atrial fibrillation\textsuperscript{4}, deep thrombophlebitis\textsuperscript{4}

**Digestive System**
- anorexia, diarrhoea, duodenal ulcer, increased appetite, thirst/dry mouth, dyspepsia, rectal disorder, eructation\textsuperscript{4}, gastrointestinal haemorrhage\textsuperscript{4}, gingivitis\textsuperscript{4}, gum haemorrhage\textsuperscript{4}, hepatomegaly\textsuperscript{4}, intestinal obstruction\textsuperscript{4}, periodontal abscess\textsuperscript{4}

**Musculoskeletal System**
- bone pain, myalgia, leg cramps\textsuperscript{4}, pathological fracture\textsuperscript{4}, ptosis\textsuperscript{4}

**Central/Peripheral Nervous System**
- paraesthesia, anxiety, delusions, depression, hypesthesia, decreased libido\textsuperscript{*}, nervousness, hyperkinesia, ataxia, hypertonia, abnormal thinking\textsuperscript{4}, amnesia\textsuperscript{4}, convulsion\textsuperscript{4}, dementia\textsuperscript{4}, confusion\textsuperscript{4}, insomnia/sleep disorders\textsuperscript{4}, neuromuscular disorders\textsuperscript{4}, neuropathy\textsuperscript{4}, paralysis\textsuperscript{4}

**Respiratory System**
- haemoptysis, epistaxis, pharyngitis, pleural effusion, pneumonia, increased cough, rhinitis, hiccup\textsuperscript{4}, voice alteration\textsuperscript{4}, asthma\textsuperscript{4}, bronchitis\textsuperscript{4}

**Skin and Appendages**
- dermatitis, hair growth, dry skin, macropapular rash, pruritus, skin discolouration

**Urogenital System**
- dysuria, frequency/urgency/impaired, haematuria, testicular pain, gynaecomastia, impotence, penis disorders, testis disorders, nocturia, urinary incontinence\textsuperscript{4}, testicular atrophy\textsuperscript{4}, bladder carcinoma\textsuperscript{4}, epididymitis\textsuperscript{4}, prostate disorder\textsuperscript{4}

**Haemic and Lymphatic System**
- anaemia, lymphoedema, decreased thromboplastin, leukocytosis, leukopenia, thrombocytopenia, lymphadenopathy\textsuperscript{4}

**Metabolic and Nutritional Disorders**
- dehydration, oedema, libido decrease, hypercholesteremia, hypokalemia, healing abnormal\textsuperscript{4}, hypoxia\textsuperscript{4}, weight loss\textsuperscript{4}

**Special Senses**
- abnormal vision, amblyopia, dry eyes, tinnitus.

**Laboratory**
- increased calcium, increased uric acid, alanine amino transferase (SGPT) increased

**Miscellaneous**
- hard nodule in throat.

\textsuperscript{*} Physiological effect of decreased testosterone.

\textsuperscript{4} These adverse reactions were only experienced by patients on Lucrin Depot 4-Month 30mg study.
In clinical trials and postmarketing surveillance, the following adverse events have been observed with this or other 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, photosensitivity reactions, swelling (temporal bone), jaundice

- **Cardiovascular System**
  - congestive heart failure, ECG changes/ischaemia, hypertension, hypotension, myocardial infarction, murmur, phlebitis/thrombosis, pulmonary emboli, sudden cardiac death, transient ischaemic attack/stroke, angina, bradycardia, cardiac arrhythmia, varicose veins, tachycardia.

- **Digestive System**
  - constipation, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, peptic ulcer, rectal polyps, diarrhoea, dry mouth, duodenal ulcer, increased appetite, liver function tests abnormal, nausea, thirst, vomiting

- **Endocrine**
  - diabetes, thyroid enlargement

- **Metabolic and Nutritional System**
  - BUN increased, calcium increased, creatinine increased, dehydration, oedema, hyperlipidaemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphatemia, hypoglycaemia, hypoproteinemia, potassium decreased, uric acid increased, bilirubin increased

- **Haemic and Lymphatic System**
  - anaemia, decreased WBC, ecchymosis, lymphedema, PT increased, PTT increased, platelets decreased, increased WBC

- **Musculoskeletal System**
  - ankylosing spondylitis, joint pain, pelvic fibrosis, tenosynovitis-like symptoms, joint disorders, myalgia, spinal fracture, paralysis

- **Nervous System**
  - anxiety, convulsion, dizziness/light-headiness, headache, hearing disorder, sleep disorders, lethargy, memory disorder, mood swings, nervousness, numbness, peripheral neuropathy, depression, delusion, hypasthenia, hypoesthesia, insomnia, libido increase, neuromuscular disorders, paresthesia, syncope/blackouts

- **Respiratory System**
  - cough, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion, dyspnea, epistaxis, hemoptysis, pharyngitis, pleural effusion, interstitial lung disease,
- **Skin and Appendages**
carcinoma of skin/ear, dry skin, hair loss, pigmentation, skin lesions, dermatitis, hair growth, hard nodule in throat, pruritus, rash, urticaria, itching

- **Urogenital System**
bladder spasms, incontinence, penile swelling, prostate pain, urinary obstruction, urinary tract infection, breast pain, breast tenderness, gynecomastia, hematuria, menstrual disorders including breakthrough and sustained vaginal bleeding, penile disorders, testicular atrophy, testicular pain, testicular size decrease, urinary disorders, urinary frequency, urinary urgency

- **Special Senses**
ophthalmologic disorders, abnormal vision, amblyopia, blurred vision, dry eyes, hearing disorders, taste disorders, tinnitus

Injection site reactions including pain, infection, inflammation, sterile abscess, induration and hematoma 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.

**Changes in Bone Density**
Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolin acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-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.

**DOSAGE AND ADMINISTRATION**
LUCRIN DEPOT 7.5 mg PDS Injection and LUCRIN DEPOT 3-Month PDS Injection and LUCRIN DEPOT 4-Month PDS Injection MUST BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN.

NOTE: Due to different release characteristics of Lucrin Depot 3-Month PDS Injection & Lucrin Depot 4-Month PDS Injection, a fractional dose of the three month depot or four month depot formulation is not equivalent to the same dose of the monthly formulation (Lucrin Depot 7.5 mg PDS Injection) and should not be given.

Similarly, fractional doses of the 4-Month formulation should not be used as a substitute for the 3-Month formulation, and multiples of the 7.5mg presentation should not be used as a substitute for the 3-Month and 4-Month formulations.

LUCRIN DEPOT 7.5mg, 3-Month, and 4-Month PREFILLED DUAL-CHAMBER SYRINGE (PDS) INJECTIONS
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 (particles) thoroughly to form a uniform suspension. The suspension will appear milky.

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, leuprorelin acetate 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.

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

OVERDOSAGE
In rats, subcutaneous administration of 250 to 500 times the recommended 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 1-mg/day dose.

For advice on the management of overdose please contact the Poisons Information Centre, phone 131126.

PRESENTATION AND STORAGE CONDITIONS
Lucrin Depot 7.5mg Prefilled Dual-Chamber Syringe (PDS) Injection is available in a single dose procedure pack of a dual chamber syringe containing sterile lyophilised microspheres of leuprorelin acetate in the front chamber and 1mL of diluent in the rear chamber. When the contents of the chambers are mixed, Lucrin Depot 7.5mg PDS is administered as a single monthly intramuscular injection.
Lucrin Depot 3-Month Prefilled Dual-Chamber Syringe (PDS) Injection is available in a single dose procedure pack of a dual chamber syringe containing sterile lyophilised microspheres of leuprorelin acetate in the front chamber and 1.5mL of diluent in the rear chamber. When the contents of the chambers are mixed, Lucrin Depot 3-Month PDS is administered as a single intramuscular injection every three months.

Lucrin Depot 4-Month Prefilled Dual-Chamber Syringe (PDS) Injection is available in a single dose procedure pack of a dual chamber syringe containing sterile lyophilised microspheres of leuprorelin acetate in the front chamber and 1.5mL of diluent in the rear chamber. When the contents of the chambers are mixed, Lucrin Depot 4-Month PDS is administered as a single intramuscular injection every four months.

Lucrin Depot 7.5 mg PDS Injection, Lucrin Depot 3-Month PDS Injection and Lucrin Depot 4-Month PDS Injection may be stored in a cool dry place where the room temperature stays below 25oC. Protect from light.

NAME AND ADDRESS OF THE SPONSOR
AbbVie Pty Ltd
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POISON SCHEDULE OF THE MEDICINE
S4

DATE OF APPROVAL
Date of TGA Approval: 14 October 2005

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