LUCRIN® DEPOT FOR INJECTION PDS 30MG

NAME OF THE MEDICINE
Non-proprietary Name
Leuprorelin acetate

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 $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ 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.

Lucrin Depot for Injection PDS 30mg contains leuprorelin acetate (30mg), polylactic acid (270.0mg), and mannitol (52.9mg). The accompanying diluent contains mannitol (50.0.mg), carboxymethylcellulose sodium (5.0mg), polysorbate 80 (1.0mg), water for injections (to 1.0mL) and glacial acetic acid to control pH.

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.

Following a single subcutaneous injection of leuprorelin acetate 30mg 6 month depot, serum levels of leuprorelin rise quickly with a subsequent decrease to a plateau within a few days. Within two hours, mean maximum serum levels of 100 ng/mL are measured. In the plateau phase, detectable serum levels were found until up to > 180 days after the last administration.

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 has not been determined.

CLINICAL TRIALS

The objective of the pivotal study EC-404 was to investigate the safety and tolerability profile of two 6-month depot dosages administered subcutaneously (22.5mg and 30.0mg leuprorelin acetate, respectively) compared to a 3-month depot (containing 11.25mg leuprorelin acetate – a European registered formulation) over a treatment period of 12 months. The efficacy of the three treatments was also evaluated.

Main inclusion criteria were male patients aged 18 – 85 years with prostate cancer, histologically confirmed by biopsy, of any grade and stage, requiring chemical castration and with a life expectancy of more than 12 months. For patients who had not received prior hormone treatment, testosterone and PSA levels at screening were to be ≥ 5.21nmol/L and ≥1 ug/L respectively (Stratum B) prior to receiving a 1 month depot to ensure hormone sensitivity. Patients receiving GnRH analogue or antiandrogen treatment for < 3 months (Stratum A) and Stratum B patients' testosterone level was to be <2.78 nmol/L prior to randomisation.

The overall response to treatment was defined as successful maintenance of suppressed testosterone serum levels without two consecutive elevations of testosterone levels >1.74 nmol/L after the first injection of the study medication until the end of the observational period at 12 months. Serum levels of testosterone, LH, FSH, PSA and leuprorelin were monitored over the course of the treatment. No differences in clinical response (as assessed by digital rectal examination, performance status, EORTC criteria or tumour staging) amongst the three doses were apparent. One Lucrin Depot 22.5mg subject was excluded due to lack of data.

Response to Treatment (Modified ITT Population)

Stratum	Treatment	Responder						Non-Responder		Total	
		<= 1.74 nmol/L		Single Point Elevation		TOTAL (responder)		Confirmed Elevation			
		N	%	N	%	N	%	N	%	N	%
Stratum A	3M depot 11.25 (n=10)	9	90.0	0	0.0	9	90.0	1	10.0	10	100.0
	6M depot 22.5 (n=23)	17	73.9	4	17.4	21	91.3	2	8.7	23	100.0
	6M depot 30 (n=28)	26	92.9	1	3.6	27	96.4	1	3.6	28	100.0
Stratum B	3M depot 11.25 (n=48)	37	77.1	1	2.1	38	79.2	10	20.8	48	100.0
	6M depot 22.5 (n=94)	69	73.4	10	10.6	79	84.0	15	16.0	94	100.0
	6M depot 30 (n=92)	75	81.5	9	9.8	84	91.3	8	8.7	92	100.0
Total	3M depot 11.25 (n=58)	46	79.3	1	1.7	47	81.0	11	19.0	58	100.0

Stratum	Treatment	Responder						Non-Responder		Total	
		<= 1.74 nmol/L		Single Point Elevation		TOTAL (responder)		Confirmed Elevation			
		N	%	N	%	N	%	N	%	N	%
	6M depot 22.5 (n=117)	86	73.5	14	12.0	100	85.5	17	14.5	117	100.0
	6M depot 30 (n=120)	101	84.2	10	8.3	111	92.5	9	7.5	120	100.0

Castration Resistant Prostate Cancer
In patients with metastatic castration-resistant prostate cancer, clinical studies have shown benefit from the addition of agents such as the androgen axis inhibitors abiraterone acetate and enzalutamide, the taxanes docetaxel and cabazitaxel, and the radiopharmaceutical Ra-223 to GnRH agonists such as leuprorelin.

INDICATIONS
Lucrin Depot for Injection PDS 30mg is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS
Lucrin Depot for Injection PDS 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 leuprorelin acetate.

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, leuprorelin acetate 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)

Although not relevant to the approved indication, leuprorelin acetate should not be administered to women with undiagnosed vaginal bleeding.

PRECAUTIONS
Initially, Lucrin Depot for Injection PDS, 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 for Injection PDS 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.

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

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 (eg those with thecal indentation, or at risk of cord compression, and patients with bladder neck obstruction).

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
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) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

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

Convulsions
Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprorelin acetate. 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
Leuprorelin acetate may reduce male and female fertility. Administration of leuprorelin acetate to male and female rats at doses of 0.024, 0.24, and 2.4 mg/kg as monthly depot formulation for up to 3 months (approximately as low as 1/30 of the human dose based on body surface area using an estimated daily dose in animals and humans) caused atrophy of the reproductive organs, and suppression of reproductive function.

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
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 for Injection PDS 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/day). 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/day 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 for Injection PDS. 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.

Prostate Cancer
See **WARNINGS,** *Effect on QT/QTc Interval.*

Effect on Laboratory Tests
Response to leuprorelin 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 on time. 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 for Injection PDS, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of Lucrin Depot for Injection PDS may be affected.

ADVERSE EFFECTS
Side effects seen with Lucrin Depot for Injection 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 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 following table presents the adverse drug reactions (ADR) and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100) not known (unable to estimate frequency based upon available data) from Lucrin 6-Month 30mg clinical studies EC-403 and EC-404 (n=151)

System Organ Class	**Preferred Term[a]**	**Frequency**
Blood and lymphatic system disorder	Anaemia	Common
Metabolism and nutrition disorders	Increased appetite	Common
	Abnormal weight gain	Uncommon
Psychiatric disorders	Libido decreased	Common
	Sleep Disorder	Uncommon
Nervous system disorders	Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Heart failure	Common
Vascular disorders	Flushing	Very common
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	Common
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
	Pruritus	Uncommon
	Night sweats	Uncommon
	Hypotrichosis	Uncommon
Renal and urinary disorders	Pollackiuria	Uncommon
	Urinary retention	Uncommon
Reproductive and breast disorders	Erectile dysfunction	Common
	Testicular atrophy	Common
	Testicular pain	Uncommon
General disorders and administration site conditions	Peripheral oedema	Uncommon
	Fatigue	Common
	Injection site reaction	Common
	Injection site inflammation	Common
	Injection site pain	Common
	Injection site induration	Common
	Injection site erythema	Very common
	Injection site abscess	Common
	Injection site swelling	Common
Investigations	Liver function test abnormal	Uncommon
	Transaminase increased	Common
[a] Depression and mood swing are commonly observed adverse reactions with long term use of GnRH agonists.		

In clinical trials and postmarketing surveillance, the following adverse reactions have been observed with this or other formulations of leuprorelin acetate. As leuprorelin has multiple indications and therefore patient populations, some of these adverse reactions may not be

applicable to every patient. For a majority of these adverse reactions, 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, serious liver injury, 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, hyperlipidemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphataemia, hypoglycaemia, hypoproteinaemia, 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 spondylosis, 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 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.

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 leuprorelin 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.

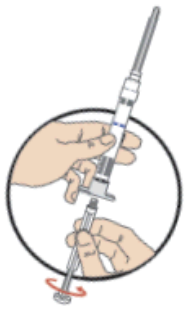
DOSAGE AND ADMINISTRATION

Leuprorelin acetate for depot suspension must be administered under the supervision of a physician.

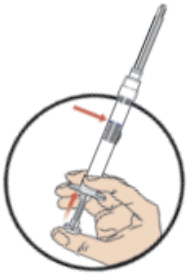
Lucrin Depot for Injection PDS 30mg is administered as a single subcutaneous injection **every six months.**

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

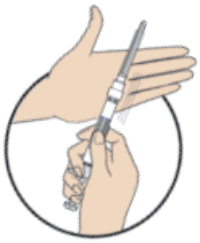
For optimal performance of the prefilled dual-chamber syringe (PDS), read and follow the following instructions:



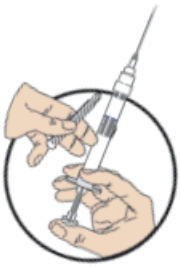
1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



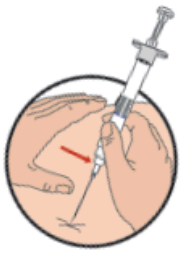
2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.



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 subcutaneously 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 approximately 133* 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.

*** Note:** As a conservative approach, the safety margin has been calculated based on the total amount of leuprorelin acetate in the highest strength formulation available and with the assumption that the drug was delivered in a single day.

PRESENTATION AND STORAGE CONDITIONS

Lucrin Depot for Injection PDS 30mg 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.

Store below 30°C. Do not refrigerate or freeze.
Store in the original container in order to protect from light.

NAME AND ADDRESS OF THE MANUFACTURER

Takeda Pharmaceutical Company Limited, Japan

CCDS03671017

Date of issue: DD MMM YYYY