Prescribing Information

NAME OF THE MEDICINAL PRODUCT

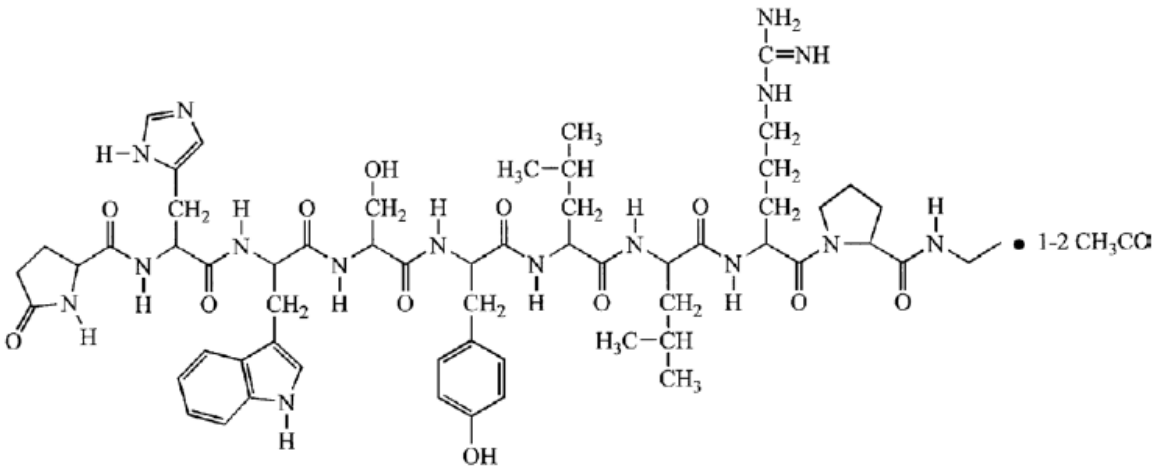
Lucrin® PDS Depot 11.25 mg

(Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg)

DESCRIPTION

Leuprorelin acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LHRH). The analogue possesses greater potency than the natural hormone.

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) and the structural formula is as follows:



Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is a formulation of leuprorelin acetate supplied as lyophilized microspheres. When mixed with diluent, it becomes a suspensionwhich is administered as an intramuscular or subcutaneous injection every three months.

Active/Inactive Ingredients

Leuprorelin Acetate Depot Suspension - 3 Month 11.25 mg contains leuprorelin acetate (11.25 mg), a polymer, polylactic acid 99.3 mg and mannitol 19.45 mg.

The compound is easily soluble in polar solutions such as water and anhydrous ethanol and propylene glycol. It is nearly insoluble in chloroform. The pH value of a solution containing 100 mg dry powder of leuprorelin acetate in one mL of solution is approximately 5 to 7.

The diluent used for reconstitution with the leuprorelin acetate powder is a clear, colorless, slightly viscous solution of carboxymethylcellulose sodium (5 mg), mannitol (50 mg), polysorbate 80 (1 mg), water for injection (1 mL) and glacial acetic acid to control pH.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Leuprorelin acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given on a continuous basis 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. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Nobel and Dunning male rats and DMBA-induced mammary tumors 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 estrone and estradiol in pre-menopausal females).

However, continuous administration of leuprorelin acetate results in decreased levels of LH and FSH and sex steroids. In males, testosterone is reduced to castrate or prepubertal levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating drug therapy at recommended doses.

Pharmacokinetics
Leuprorelin acetate is not active when given orally. Bioavailability of this agent following subcutaneous administration is comparable to that after intramuscular administration.

Absorption
Following a single administration of Leuprorelin Acetate Depot Suspension - 3 Month 11.25 mg, a rapid increase of leuprorelin acetate concentration was observed. A mean peak leuprorelin plasma concentration of 21.82 (± 11.24) ng/mL was observed three hours after injection. Leuprorelin acetate reached plateau levels within 7 to 14 days after injection. At week 4, a mean leuprorelin plasma concentration of 0.26 (± 0.10) ng/mL was noted. It then declined to a mean leuprorelin plasma concentration of 0.17 (± 0.08) ng/mL at 12 weeks.

Following a single injection of the three month formulation of leuprorelin acetate depot suspension 11.25 mg in female subjects, a mean plasma leuprorelin concentration of 36.3 ng/mL was observed at 4 hours. Leuprorelin appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean level then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprorelin concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprorelin and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steadystate level, was similar to the release pattern seen with the monthly formulation.

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

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

Animal studies have shown ^{14}C-labeled leuprorelin was metabolized into smaller inactive peptides, a pentapeptide (Metabolite I) tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further metabolized.
The major metabolite (M-I) plasma concentrations measured in five prostate cancer patients given leuprorelin acetate depot suspension reached a maximum concentration two to six hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprorelin concentrations.

Excretion
Following administration of Leuprorelin Acetate for Depot Suspension 3.75 mg to three patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine over 27 days.

Special Populations

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

INDICATIONS

Prostate Cancer

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is indicated in the palliative treatment of advanced prostatic cancer.

It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

Endometriosis

Leuprorelin Acetate for Depot Suspension 3 month 11.25 mg is indicated in the treatment of endometriosis for a period of six months. It can be used as sole therapy or as an adjunct to surgery.

Uterine Fibroids

Leuprorelin Acetate for Depot Suspension 3 month 11.25 mg is also indicated in the treatment of leiomyoma uteri (uterine fibroids) for a period up to six months. Therapy may be preoperative prior to myomectomy or hysterectomy, or it may provide symptomatic relief for the perimenopausal woman who does not desire surgery.

Breast Cancer

Leuprorelin Acetate for Depot Suspension - 3 month 11.25 mg is also indicated for the treatment of breast cancer in pre- and peri-menopausal women in whom hormone therapy is specified.

CONTRAINDICATIONS

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is contraindicated in patients with known hypersensitivity to leuprorelin acetate, similar nonapeptides, or any of the excipients.

Isolated cases of anaphylaxis have been reported with the monthly formulation of Leuprorelin Acetate for Depot Suspension.

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is not suitable for the treatment of patients following an orchiectomy.

Undiagnosed abnormal vaginal bleeding.

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is contraindicated in women who are or may become pregnant while receiving the drug.

Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprorelin acetate in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that fetal abnormalities and spontaneous abortion may occur if the drug is administered during pregnancy

Use in women who are breastfeeding.(see Nursing Mothers section).

WARNINGS and PRECAUTIONS

All Populations

As the effect of Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is present throughout the course of therapy, the drug should only be used in patients who require hormonal suspension for at least three months.

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

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 changes can occur during any hypoestrogenic state in women and in long-term use in prostate cancer in men. There is no data in men regarding reversibility after withdrawal of leuprorelin acetate. In women, bone mineral density loss may be reversible after withdrawal of leuprorelin acetate. (see **ADVERSE REACTIONS)**

Convulsions

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.

Men

Prostate Cancer
Isolated cases of worsening signs and symptoms during the first few weeks of treatment have been reported with GnRH analogs. 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 ureteric obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications Worsening of symptoms may contribute to paralysis with or without fatal complications.
For patients at risk, the physician may consider initiating therapy with daily 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 urinary tract obstruction should be closely observed during the first few weeks of therapy

Hyperglycemia and an increased risk of developing diabetes havebeen reported in men receiving GnRH agonists. Hyperglycemia mayrepresent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/orglycosylated hemoglobin (HbA1c) periodically in patients receivingGnRH agonists, and manage with current practice for treatment of hyperglycemia or diabetes.

Increased risk of developing myocardial infarction, sudden cardiacdeath and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving 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.

Laboratory Tests

Response to leuprorelin acetate should be monitored by measuring serum levels of testosterone, as well as prostate specific antigen and prostatic acid phosphatase. 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. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections on time. Transient increases in acid phosphatase levels sometimes occurred early in treatment. However, by the fourth week, the elevated levels usually decrease to values at or near baseline.

Women

Endometriosis/Uterine Fibroids
During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy at adequate doses. However, reports of heavy vaginal bleeding requiring medical or surgical intervention with continued therapy have been reported in the treatment of submucous leiomyoma uteri.

Safe use of leuprorelin acetate in pregnancy has not been established clinically. Before starting 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 nonhormonal method of contraception should be used.

Since bone loss can be anticipated as part of natural menopause, it may also be expected to occur during a medically-induced hypoestrogenic state. Bone loss has been found to be reversible after completion of a six month course of leuprorelin acetate. Experience with Leuprorelin Acetate for Depot Suspension in females has been limited to women 18 years of age and older, treated for 6 months.

Laboratory Tests
Response to leuprorelin acetate should be monitored one to two months after the start of therapy with a GnRH stimulation test and sex steroid levels. Measurement of bone age for advancement should be done every 6 to 12 months.
Sex steroids may increase or rise above pre-pubertal levels if the dose is inadequate. Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

Drug Interactions
No pharmacokinetic-based drug-drug interaction studies have been conducted with Leuprorelin Acetate Depot Suspension. However, because leuprorelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions
Administration of leuprorelin acetate depot in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after leuprorelin acetate depot treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of leuprorelin acetate depot may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no

leuprorelin acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprorelin acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

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

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

Pregnancy
See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**

LactationIt is not known whether leuprorelin acetate is excreted in human milk. Therefore, *not be used by* nursing mothers.

ADVERSE REACTIONS

The following adverse events are commonly associated with the pharmacological actions of leuprorelin acetate on the steroidogenesis:

Men:

Neoplasm benign, malignant and unspecified (including cysts and polyps): prostate tumor flare, aggravation of prostate cancer
Metabolism and nutrition disorders: weight gain, weight loss
Psychiatric disorders: Loss or decreased libido, increase libido
Nervous system disorders: headache, muscular weakness
Vascular disorders: vasodilatation, hot flushes, hypotension, orthostatic hypotension
Skin and subcutaneous tissue disorders: dry skin, hyperhydrosis, rash, urticaria, hair growth abnormal, hair disorder, night sweats, hypotrichosis, pigmentation disorder, cold sweat, hirsutism
Reproductive system and breast disorders: gynaecomastia, breast tenderness, erectile dysfunction, testicular pain, breast enlargement, breast pain, prostate pain, penile swelling, penis disorder, testis atrophy
General disorders and administration site conditions: mucosal dryness
Investigations: PSA increased, bone density decreased
Long exposure (6 to 12 months): Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis.

Women:

Metabolism and nutrition disorders: weight gain, weight loss
Psychiatric disorders: Loss or decreased libido, increased libido, affects lability
Nervous system disorders: headache
Vascular disorders: hot flushes, vasodilatation, hypotension
Skin and subcutaneous tissue disorders: acne, seborrhea, dry skin, urticaria, skin odour

abnormal, hyperhydrosis, hair growth abnormal, hirsutism, hair disorder, eczema, nail disorder, night sweats

Reproductive system and breast disorders: vaginal haemorrhage, dysmenorrhea, menstrual disorder, breast enlargement, breast engorgement, breast atrophy, genital discharge, vaginal discharge, galactorrhea, breast pain, metrorrhagia, menopausal symptoms, dyspareunia, uterine disorder, vaginitis, menorrhagia

General disorders and administration site conditions: feeling hot, irritability

Investigations: bone density decreased

Long exposure (6 to 12 months): Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis.

Clinical and Postmarketing:

The following sections present adverse events seen in clinical studies or postmarketing experience. They are arranged by patient populations: Men, Women, Children.

Men:

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.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a 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 (see **WARNINGS and PRECAUTIONS**).

Table 1 presents all 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 prostate cancer clinical studies and post marketing experience. A blank indicates that the ADR was not seen from that particular source.

TABLE 1: Prostate Cancer

		Prostate Cancer **11.25 mg**	Post Marketing
System Organ Class	**Preferred Term**	**Frequency**	**Frequency**
Infections and infestations	Infection		Not Known
	Bronchitis	Common	
	Urinary tract infection	common	Not Known
	Infected cyst	Uncommon	
	Viral infection	Uncommon	
	Candidiasis	Uncommon	
	Sepsis	Uncommon	
	Pharyngitis		Not Known
	Pneumonia		Not Known

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pseudolymphoma	Uncommon	
	Skin cancer		Not Known
Blood and lymphatic system disorder	Anaemia	Common	Not Known
	Eosinophilia	Uncommon	
Immune system disorders	Hypersensitivity	Uncommon	
	Anaphylactic reaction		Not Known
Endocrine disorder	Goiter		Not Known
	Pituitary apoplexy		Not Known
Metabolism and nutrition disorders	Anorexia	Common	
	Diabetes mellitus		Not Known
	Increased appetite		Not Known
	Hyperglycaemia	Uncommon	
	Hypoglycaemia	Uncommon	Not Known
	Dehydration	Uncommon	Not Known
	Hyperlipidaemia		Not Known
	Hyperphosphatemia		Not Known
	Hypoproteinemia		Not Known
	Abnormal weight gain	Very common	
	Abnormal loss of weight	Common	
Psychiatric disorders	Mood swings		Not Known
	Nervousness		Not Known
	Libido decreased	Very common	
	Libido increased		Not Known
	Insomnia	Common	Not Known
	Sleep disorder		Not Known
	Depression	Common	Not Known
	Anxiety		Not Known
	Delusion		Not Known
	Suicidal ideation		Not Known
	Suicidal attempt		Not Known
Nervous system disorders	Dizziness	Uncommon	Not Known
	Headache	Common	Not Known
	Paraesthesia	Common	Not Known
	Lethargy		Not Known
	Somnolence	Uncommon	
	Memory Impairment		Not Known

	Dysgeusia		Not Known
	Hypoaesthesia		Not Known
	Syncope		Not Known
	Tremor	Uncommon	
	Simple partial seizures	Uncommon	
	Neuropathy peripheral		Not Known
	Cerebrovascular accident		Not Known
	Loss of consciousness		Not Known
	Transient ischemic attack		Not Known
	Paralysis		Not Known
	Neuromyopathy		Not Known
	Convulsion		Not Known
Eye disorders	Vision blurred		Not Known
	Eye disorder		Not Known
	Visual impairment		Not Known
	Amblyopia		Not Known
	Dry eye		Not Known
Ear and labyrinth disorders	TInnitus		Not Known
	Hearing impaired		Not Known
Cardiac disorders	Cardiac failure congestive		Not Known
	Arrhythmia		Not Known
	Myocardial infraction		Not Known
	Angina pectoris	Uncommon	Not Known
	Tachycardia		Not Known
	Cardiac failure	Uncommon	
	Bradycardia	Uncommon	Not Known
	Sudden cardiac death		Not Known
	Atrioventricular block	Uncommon	
Vascular disorders	Hot flush	Very common	
	Lymphoedema	Common	Not Known
	Hypertension	Common	Not Known
	Thrombophlebitis	Common	
	Phlebitis		Not Known
	Thrombosis		Not Known
	Aneurysm	Uncommon	
	Circulatory collapse	Uncommon	
	Flushing	Uncommon	
	Haematoma	Uncommon	
	Hypotension		Not Known
	Varicose vein		Not Known
Respiratory, thoracic and mediastinal disorders	Pleural rub		Not Known
	Pulmonary fibrosis		Not Known
	Epistaxis		Not Known
	Dyspnoea	Common	Not Known
	Haemoptysis		Not Known
	Cough	Uncommon	Not Known
	Asthma	Common	

	Chronic obstructive pulmonary disease	Uncommon	
	Pleural effusion		Not Known
	Lung infiltration		Not Known
	Respiratory disorder		Not Known
	Sinus congestion		Not Known
	Pulmonary embolism		Not Known
	Interstitial lung disease		Not Known
Gastrointestinal disorders	Constipation	Common	Not Known
	Nausea	Common	Not Known
	vomiting		Not Known
	Gastritis	Uncommon	
	Gastrointestinal haemorrhage		Not Known
	Abdominal distention		Not Known
	Diarrhea		Not Known
	Dysphagia		Not Known
	Dry mouth		Not Known
	Duodenal ulcer		Not Known
	Gastrointestinal disorder		Not Known
	Peptic ulcer		Not Known
	Rectal polyp		Not Known
Hepato-biliary disorder	Hepatic function abnormal		Not Known
	Hepatitis cholestatic	Uncommon	
	Hepatocellular injury	Uncommon	
	Jaudice		Not Known
Skin and subcutaneous tissue disorders	Alopecia	Uncommon	Not Known
	Ecchymosis		Not Known
	Rash	Uncommon	Not Known
	Dry skin	Uncommon	Not Known
	Photosensitivity reaction		Not Known
	Urticaria		Not Known
	Hyperhidrosis	Very common	
	Dermatitis		Not Known
	Hair growth abnormal		Not Known
	Pruritus	Common	Not Known
	Pigmentation disorder		Not Known
	Skin lesion		Not Known
Musculoskeletal and connective tissue disorders	Bone pain	Very common	
	Myalgia	Uncommon	Not Known
	Bone swelling		Not Known

	Arthropathy		Not Known
	Arthralgia	Common	Not Known
	Back pain	Common	
	Muscular weakness	common	
	Pain in extremity	Common	
	Muscle spasms	Uncommon	
	Ankylosing spondylitis		Not Known
	Tenosynovitis		Not Known
Renal and urinary disorders	Urinary incontinence	Uncommon	Not known
	Dysuria	Common	
	Pollakiuria	Uncommon	Not Known
	Micturition urgency		Not Known
	Haematuria	Common	Not known
	Nocturia	Very common	
	Urinary retention	Uncommon	
	Micturition disorder	Uncommon	
	Bladder spasm		Not Known
	Urinary tract disorder		Not Known
	Urinary tract obstruction		Not Known
Reproductive system and breast disorders	Gynaecomastia	Common	Not Known
	Breast tenderness		Not Known
	Erectile dysfunction	Very common	
	Testicular atrophy		Not Known
	Testicular pain		Not Known
	Breast pain		Not Known
	Testicular disorder	Very common	Not Known
	Penile swelling		Not Known
	Penis disorder		Not Known
	Prostatic pain		Not Known
General disorders and administration site conditions	Pain	Common	Not Known
	Chest pain	Uncommon	
	Oedema		Not Known
	Oedema peripheral	Common	
	Gravitational oedema	Uncommon	
	Application site oedema	Common	
	Mucosal dryness	Uncommon	
	Asthenia	Common	Not Known
	Fatigue	Very common	
	Pyrexia		Not Known
	Injection site reaction	Very common	Not Known
	Injection site inflammation		Not Known
	Injection site mass	Common	
	Injection site pain	Common	Not Known
	Injection site induration		Not Known

	Injection site abscess sterile		Not Known
	Injection site hematoma		Not Known
	Chills		Not Known
	Nodule		Not Known
	Thirst		Not Known
	Malaise	Uncommon	
	Influenza like illness	Common	
	Gait disturbance	Uncommon	
	Inflammation		Not Known
	Pelvic fibrosis		Not Known
Investigations	Blood urea increased		Not Known
	Blood uric acid increased		Not Known
	Blood creatinine increased		Not Known
	Red blood cell sedimentation rate increased	Uncommon	
	Blood calcium increased		Not Known
	Blood alkaline phosphatase increased	Common	
	Blood lactic dehydrogenase increased	Common	
	Prostatic Specific Antigen increased	Common	
	Alanine aminotransferase increased/ALT	Common	
	Aspartate aminotransferase increased/AST	Common	
	Gamma-glutamyltransferase increased	Common	
	Electrocardiogram abnormal	Common	Not Known
	ECG signs of myocardial ischemia		Not Known
	Blood testosterone increased	Uncommon	
	Liver function test abnormal		Not Known
	Platelet count decreased		Not Known
	Blood potassium decreased		Not Known
	White blood cell count	Uncommon	Not Known

	increased		
	White blood cell count decreased		Not Known
	Prothrombin time prolonged		Not Known
	Activated partial thromboplastin time prolonged		Not Known
	Cardiac murmur		Not Known
	Low density lipoprotein increased		Not Known
	Blood triglycerides increased		Not Known
	Blood bilirubin increased		Not Known
Injury, poisoning and procedural complications	Fracture	Uncommon	
	Spinal fracture		Not Known
	Head injury	Uncommon	
	Fall	Uncommon	
	Device occlusion	Uncommon	
Surgical and medical procedures	Tumor excision	Uncommon	
	Transurethral bladder resection	Uncommon	
	Lithotripsy	Uncommon	

Women:
Table 2 presents ADRs 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 endometriosis, uterine fibroid and breast cancer clinical studies and postmarketing experience. A blank indicates that the ADR was not seen from that particular source.

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism,myocardial infarction, stroke, and transient ischemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH agonist and these events

Changes in Bone Density
In controlled clinical studies, patents with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with leuprorelin depot 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.9% at six months compared with the pretreatment value. For those patents who were tested at six or twelve months after discontinuation of therapy, mean bone density returned to within 2% of pretreatment. When leuprorelin depot 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed.

Table 2: Women Indications
FEMALE INDICATION ADRs

		Endo (11.25)	Fibroids (11.25)	BC (11.25)	Post marketing
System Organ Class	**PT**	**Frequency**	**Frequency**	**Frequency**	**Frequency**
Infections and infestations	Infection	Uncommon			Not Known
	Rhinitis		Uncommon		
	upper respiratory tract infection			Uncommon	
	pyelonephritis	Uncommon			
	furuncle	Uncommon			
	Urinary tract infection				Not Known
	Vulvovaginal candidiasis		Uncommon		
	Influenza		Uncommon		
	Pharyngitis				Not Known
	Pneumonia				Not Known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer				Not Known
Blood and lymphatic system disorder	Leukopenia			Uncommon	
	Anaemia				Not Known
Immune system disorders	Anaphylactic reaction				Not Known
Endocrine disorders	Goiter				Not Known
	Pituitary apoplexy				Not Known
Metabolism and nutrition disorders	Anorexia	Uncommon		Uncommon	
	Diabetes mellitus				Not Known
	Increased appetite	Uncommon	Uncommon	Very common	Not Known
	Decreased appetite			Common	
	Hypoglycaemia				Not Known
	Dehydration				Not Known
	Hyperlipidaemia				Not Known
	Hypercholesterolaemia	Common			
	Hyperphosphatemia				Not Known
	Hypoproteinemia				Not Known
	Abnormal weight gain	Very common	Common	Very common	
	Abnormal loss of weight	Common	Common	Very common	

Psychiatric disorders	Affect lability	Very common	Common		
	Mood swings			Very common	Not Known
	Personality disorder	Uncommon			
	Nervousness	Very common	Common	Very common	Not Known
	Libido decreased	Very common	Common		
	Libido increased				Not Known
	Insomnia	Very common	Common	Very common	Not Known
	Sleep disorder			Common	Not Known
	Depression	Very common	Common	Very common	Not Known
	Major depression	Common			
	anxiety	Common	Uncommon		Not Known
	delusion	Uncommon			Not Known
	thinking abnormal	Uncommon			
	confusional state	Common			
	euphoric mood	Uncommon (euphoria)			
	hostility	Common			
	apathy	Uncommon			
	Nervousness/anxiety	Very common			
	Suicide ideation				Not Known
	Suicide attempt				Not Known
Nervous system disorders	dizziness	Very common	Common	Very common	Not Known
	dizziness postural			Common	
	headache	Very common	Very common	Very common	Not Known
	paraesthesia	Common	Common	Common	Not Known
	Lethargy				Not Known
	somnolence	Uncommon		Common	
	memory impairment			Common	Not Known
	amnesia	Uncommon			
	dysgeusia		Uncommon		Not Known
	hypoaesthesia			Common	Not Known
	syncope	Uncommon			Not Known
	migraine	Common	Uncommon		
	hypertonia	Common	Common		
	ataxia	Uncommon			
	Tremor			Common	
	Neuropathy peripheral				Not Known
	Cerebrovascular accident				Not Known
	Loss of consciousness				Not Known
	Transient ischemic attack				Not Known
	Paralysis				Not Known
	Neuromyopathy				Not Known
	Convulsion				Not Known
Eye disorders	Vision blurred				Not Known
	eye disorder	Uncommon			Not Known
	visual impairment	Common			Not Known
	amblyopia	Common			Not Known
	eye pain	Uncommon			
	conjunctivitis		Uncommon	Common	
	Dry eye				Not Known
Ear and labyrinth disorders	vertigo	Common			

	deafness			Common	
	motion sickness			Common	
	auricular swelling			Common	
	Tinnitus				Not Known
	Hearing impaired				Not Known
Cardiac disorders	Cardiac failure congestive				Not Known
	Arrhythmia				Not Known
	Myocardial infraction				Not Known
	Angina pectoris				Not Known
	tachycardia	Uncommon	Uncommon		Not Known
	palpitations	Common		Common	
	Bradycardia				Not Known
Vascular disorders	hot flush			Very common	
	Vasodilatation	Very common	Very common		
	Lymphoedema				Not Known
	Hypertension				Not Known
	Phlebitis				Not Known
	Thrombosis				Not Known
	Hypotension				Not Known
	Varicose vein				Not Known
Respiratory, thoracic and mediastinal disorders	Pleural rub				Not Known
	Pulmonary fibrosis				Not Known
	Epistaxis	Uncommon		Common	Not Known
	Dyspnoea			Common	Not Known
	Haemoptysis				Not Known
	dysphonia	Uncommon			
	sputum increased			Common	
	cough			Common	Not Known
	Pleural effusion				Not Known
	Lung infiltration				Not Known
	Respiratory disorder				Not Known
	Sinus congestion				Not Known
	Pulmonary embolism				Not Known
	Interstitial lung disease				Not Known
Gastrointestinal disorders	constipation	Common	Uncommon	Common	Not Known
	nausea	Very common	Common	Very common	Not Known
	vomiting		Uncommon	Common	Not Known
	nausea and vomiting	Common	Uncommon		
	Gastrointestinal haemorrhage				Not Known
	abdominal distention	Uncommon		Common	Not Known
	diarrhoea	Common	Common	Common	Not Known
	Dysphagia				Not Known
	Gingivitis			Common	
	dyspepsia	Uncommon			
	flatulence	Uncommon	Common		
	gastritis	Uncommon		Common	
	gingival bleeding	Uncommon			
	dry mouth	Common	Uncommon		Not Known
	Abdominal pain	Common	Common		

	abdominal pain upper			Common	
	abdominal pain lower			Common	
	stomatitis			Common	
	retching			Common	
	Duodenal ulcer				Not Known
	Gastrointestinal disorder				Not Known
	Peptic ulcer				Not Known
	Rectal polyp				Not Known
Hepato-biliary disorder	liver tenderness	Uncommon			
	hepatic function abnormal			Common	Not Known
	Serious liver injury				Not Known
	hepatic steatosis			Common	
	Jaundice				Not Known
Skin and subcutaneous tissue disorders	erythema			Common	
	alopecia	Common		Common	Not Known
	Ecchymosis				Not Known
	Acne	Very common		Common	
	Seborrhoea	Common			
	Rash	Common	Common	Common	Not Known
	Rash maculo-papular	Uncommon			
	dry skin	Common	Common		Not Known
	photosensitivity reaction	Uncommon			Not Known
	Urticaria				Not Known
	Skin odour abnormal		Uncommon		
	Hyperhidrosis	Common	Common	Very common	
	Dermatitis				Not Known
	Hair growth abnormal				Not Known
	hirsutism	Common	Uncommon		
	Hair disorder	Uncommon			
	Eczema			Common	
	Pruritus				Not Known
	nail disorder		Uncommon		
	skin discolouration		Uncommon		
	dermatitis bullous		Uncommon		
	Pigmentation disorder				Not Known
	Skin lesion				Not Known
Musculoskeletal and connective tissue disorders	bone pain			Common	
	myalgia	Uncommon	Uncommon		Not Known
	Bone swelling				Not Known
	Arthropathy	Common	Common		Not Known
	Arthralgia	Common	Common	Very common	Not Known
	back pain	Common	Common	Very common	
	osteoarthritis			Common	
	arthritis	Uncommon			
	nuchal rigidity	Common			
	neck pain	Common		Common	
	muscular weakness			Common	
	musculoskeletal stiffness			Common	
	muscle twitching			Common	
	Ankylosing spondylitis				Not Known

	Tenosynovitis				Not Known
Renal and urinary disorders	Urinary incontinence	Uncommon			Not Known
	Dysuria	Common			
	Pollakiuria	Uncommon		Common	Not Known
	Micturition urgency				Not Known
	Hematuria				Not Known
	Bladder spasm				Not Known
	Urinary tract disorder				Not Known
	urinary tract obstruction				Not Known
Reproductive system and breast disorders	Gynaecomastia				Not Known
	Breast tenderness				Not Known
	Vaginal haemorrhage				Not Known
	Menstrual disorder		Uncommon		Not Known
	Breast enlargement	Uncommon			
	breast engorgement	Uncommon			
	breast atrophy	Common			
	Genital discharge	Common			
	vaginal discharge			Common	
	galactorrhoea	Uncommon			
	breast pain	Common	Common	Common	Not Known
	pelvic pain	Common	Uncommon		
	metrorrhagia		Uncommon	Common	Not Known
	Menopausal symptoms			Common	
	Vaginitis	Very common	Very common	Common	
	Menorrhagia		Uncommon		
General disorders and administration site conditions	Pain	Common	Common		Not Known
	chest pain	Common	Uncommon	Common	
	oedema	Common	Uncommon	Common	Not Known
	Oedema peripheral	Common	Common	Common	
	face oedema	Uncommon			
	generalised oedema	Uncommon			
	asthenia	Common	Common	Very common	Not Known
	fatigue			Common	
	pyrexia			Common	Not Known
	Injection site reaction	Uncommon		Common	Not Known
	Injection site inflammation				Not Known
	Injection site mass	Uncommon	Uncommon		
	Injection site pain	Common	Common	Very common	Not Known
	injection site induration			Very common	Not Known
	injection site pruritus			Common	
	injection site erythema			Common	
	Injection site abscess sterile				Not Known
	Injection site hematoma				Not Known
	Chills	Common	Common		Not known
	Nodule				Not Known
	Injection site hypersensitivity	Uncommon			
	thirst	Common			Not Known
	general physical health deterioration			Very common	
	feeling hot			Very common	

	irritability			Common	
	malaise			Common	
	condition aggravated		Uncommon (aggravation rxn)		
	Inflammation				Not Known
	Pelvic fibrosis				Not Known
Investigations	Blood urea increased				Not Known
	Blood uric acid increased				Not Known
	Blood creatinine increased				Not Known
	Blood calcium increased				Not Known
	body temperature increased			Uncommon	
	occult blood positive			Common	
	Electrocardiogram abnormal				Not Known
	ECG signs of myocardial ischemia				Not Known
	liver function test abnormal		Common		Not Known
	Platelet count decreased				Not Known
	Blood potassium decreased				Not Known
	White blood cell count increased				Not Known
	White blood cell count decrease				Not Known
	Prothrombin time prolonged				Not Known
	Activated partial thromboplastin time prolonged				Not Known
	laboratory test abnormal		Uncommon		
	Cardiac murmur				Not Known
	Low density lipoprotein increased				Not Known
	Blood triglycerides increased				Not Known
	Blood bilirubin increased				Not Known
	procedural pain			Common	
Injury, poisoning and procedural complications	Spinal fracture				Not Known

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose of leuprorelin acetate depot suspension. In animal studies, doses of up to 500 *approximately 133* times the recommended human dose resulted in dyspnea, decreased activity and local irritation at the injection site. In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

General
Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg must be administered under the supervision of a physician.

Upon reconstitution, the suspension should be discarded if not used immediately. the suspension should be discarded if not used

immediately.

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

Reconstitute the microspheres immediately prior to administration
The recommended dose of Leuprorelin Acetate Depot Suspension - 3 Month 11.25 mg is 11.25 mg, administered as a single subcutaneous or intramuscular injection **every three months**.

Use in treatment of endometriosis
It is recommended that the therapy begin with the first day of the menstrual cycle after pregnancy has been ruled out. Development of amenorrhea is usually evidence of a clinical response, although spotting or bleeding from the atrophic endometrium can still occur.

Use in treatment of uterine fibroids
Recommended duration of therapy is up to 6 months.

Preparation for Administration

Leuprorelin

Leuprorelin Acetate Prefilled Dual Chamber Syringe (PDS):
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 intramuscularly or subcutaneously at the time of the reconstitution. The suspension settles very quickly following reconstitution; therefore, leuprorelin acetate should be mixed and used immediately.

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

STORAGE
The shelf life for this product is 36 months unopened. Do not store above 25°C. Once reconstituted with the sterile diluent, the suspension should be administered immediately. Protect from freezing.

HOW SUPPLIED
Leuprorelin Acetate PDS – 3 Month 11.25mg is available in a single dose administration kit of a syringe containing sterile lyophilized microspheres which are leuprorelin acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1 mL of diluent, Leuprorelin Acetate PDS – 3 Month 11.25mg is administered as a single subcutaneous or intramuscular injection.

Manufacturer: Takeda Japan, For Abbott Laboratories, Spain

License Holder: Abbott Laboratories, Israel

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in