LUCRIN® DEPOT
11.25mg

STERILE LEUPRORELIN ACETATE FOR DEPOT SUSPENSION – 3 MONTH

DESCRIPTION

Leuprorelin acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog 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). During the manufacture of leuprorelin acetate depot suspension, acetic acid is lost leaving the peptide.

Leuprorelin acetate for depot suspension 3-Month (11.25mg) is a formulation of leuprorelin acetate supplied in a prefilled dual chamber syringe containing sterile lyophilised microspheres. When mixed with diluent, it becomes a suspension which is administered as an intramuscular or subcutaneous injection every 3 months.

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 front chamber of Lucrin Depot Prefilled Dual Chamber Syringe contains leuprorelin acetate (11.25 mg), polylactic acid (99.3 mg), and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, Ph Eur, and glacial acetic acid, Ph Eur to control pH.

INDICATIONS

Prostate Cancer

Leuprorelin acetate for depot suspension 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.

In clinical trials, the safety and efficacy of leuprorelin acetate for depot suspension does not differ from that of the daily subcutaneous injection dosage.

Endometriosis

Leuprorelin acetate for depot suspension 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. Leuprorelin acetate for depot suspension with norethisterone 5mg daily as add-back is also indicated for treatment of endometriosis for a period of six months.

Uterine Fibroids

Leuprorelin acetate for depot suspension is also indicated in the treatment of leiomyoma uteri (uterine fibroids), as a pre-operative treatment only, for a period up to six months.

Breast Cancer

Leuprorelin acetate for depot suspension is indicated for the treatment of breast cancer in pre- and peri-menopausal women in which hormone therapy is specified.

DOSAGE AND ADMINISTRATION

General

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

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

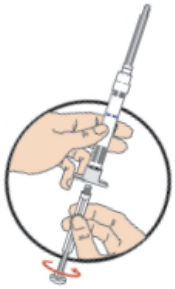
Since the product does not contain a preservative, the suspension should be discarded if not used immediately.

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.

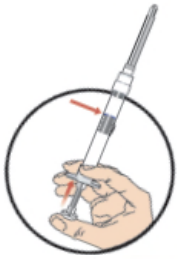
The recommended dose of leuprorelin acetate for depot suspension (11.25 mg) is 11.25 mg, administered as a single subcutaneous or intramuscular injection **every three months**.

Preparation for Administration

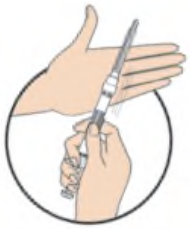
For optimal performance of the Prefilled Dual Chamber Syringe (PDS), read and follow the following instructions:



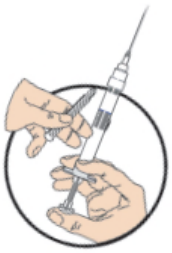
1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



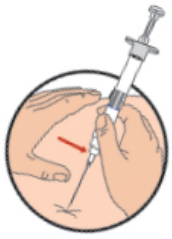
2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.



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 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 a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent hub of the needle.

CONTRAINDICATIONS
Leuprorelin acetate 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.

Leuprorelin acetate is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3* of the human dose) to rabbits, leuprorelin acetate (Depot Formulation) produced a dose-related increase in major fetal abnormalities. 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 the monthly formulation 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 spontaneous abortion may occur if the drug is administered during pregnancy.

*** NOTE:** the safety margin has been calculated based on the estimated average daily release of leuprorelin acetate from the depot formulation both for human and animals. An overall safety margin has been used that is expected to represent all of the leuprorelin acetate formulations worldwide adequately.

Leuprorelin acetate should not be administered to patients with undiagnosed vaginal bleeding.

WARNINGS AND PRECAUTIONS

All Populations

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

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.

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.

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**: Women).

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.

Men

Prostate Cancer
Initially, leuprorelin acetate, 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 leuprorelin acetate for depot suspension treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonist, 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, initiation of therapy with daily leuprorelin acetate injection for the first two weeks to facilitate withdrawal of treatment may be considered. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

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

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

Laboratory Tests
Response to leuprorelin acetate should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen. 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. Castrate levels were reached within two to four weeks and once achieved were maintained in most patients for as long as the patients received their injections on time.

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. No data are available for women receiving the drug for a longer interval.

DRUG INTERACTIONS

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprorelin acetate. 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.

Prostate Cancer

See **WARNINGS AND PRECAUTIONS,** Men, *Effect on QT/QTc Interval.*

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.

PREGNANCY AND LACTATION

Pregnancy

See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**: Women.

Lactation

It is not known whether leuprorelin acetate is excreted in human milk. Therefore, it should not be used by nursing mothers.

ADVERSE REACTIONS

The following adverse reactions are commonly associated with the pharmacological actions of leuprorelin acetate on 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, increased 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 sweats, 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, affect 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, vulvovaginitis, 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 reactions seen in clinical studies or postmarketing experience. They are arranged by patient populations: Men and Women

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.

As leuprorelin acetate has multiple indications, and therefore patient populations, some of these postmarketing 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.

Table 1: Prostate Cancer

		11.25 mg / 3 month (EC001, EC002, n=181)	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 disorders	Goiter		Not known
	Pituitary apoplexy		Not known
Metabolism and nutrition disorders	Anorexia	Common	
	Diabetes mellitus		Not known
	Increased appetite		Not known
	Hyperglycemia	Uncommon	
	Hypoglycemia	Uncommon	Not known
	Dehydration	Uncommon	Not known
	Hyperlipidaemia		Not known
	Hyperphosphataemia		Not known
	Hypoproteinaemia		Not known
	Abnormal weight gain	Very common	
	Abnormal loss of weight	Common	
Psychiatric disorders	Mood swings[a]		Not known
	Nervousness		Not known
	Libido decreased	Very common	
	Libido increased		Not known
	Insomnia	Common	Not known
	Sleep disorder		Not known
	Depression[a]	Common	Not known
	Anxiety		Not known
	Delusion		Not known
	Suicidal ideation		Not known
	Suicide 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 infarction		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 hemorrhage		Not known
	Abdominal distention		Not known
	Diarrhoea		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 disorders	Hepatic function abnormal		Not known
	Hepatitis cholestatic	Uncommon	
	Heptocellular injury	Uncommon	
	Serious liver injury		Not known
	Jaundice		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 haematoma		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
	RBC sedimentation rate increased	Uncommon	
	Blood Ca increased		Not known
	Blood alkaline phosphatase increased	Common	
	Blood LDH increased	Common	
	PSA increased	Common	
	ALT increased	Common	
	AST increased	Common	
	GGT increased	Common	
	ECG abnormal	Common	Not known
	ECG signs of myocardial		Not known

	ischemia		
	Blood testosterone increased	Uncommon	
	LFT abnormal		Not known
	Platelet count decreased		Not known
	Blood K decreased		Not known
	WBC count increased		Not known
	WBC count decreased		Not known
	PT prolonged		Not known
	APTT prolonged		Not known
	Cardiac murmur		Not known
	LDL increased		Not known
	Blood TG 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	
[a] Depression and mood swing are commonly observed adverse reactions with long term use of GnRH agonists.			

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 post-marketing experience. A blank indicates that the ADR was not seen from that particular source.

As leuprorelin acetate has multiple indications, and therefore patient populations, some of these postmarketing adverse reactions may not be applicable to every patient. For a majority of these reactions, a cause and effect relationship has not been established.
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, patients 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 3.2% at six months compared with the pretreatment value. For those patients 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 fibroids 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. Use of Lucrin Depot for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known factors for decreased bone mineral content may cause additional bone loss **and is not recommended.**

Table 2: Women Indications

		Endo (3.75, 11.25: M86-031, M86-039, n=166)	**Fibroids (3.75, 11.25: M86-034, M86-049, M86-062, M90-411, n=167)**	**BC (11.25: CPH-101, B02/EC 008, n=365)**	**Addback (3.75, 11.25: M92-878, M97-777, n=191)**	**Post Marketing**
System organ class	**Preferred Term**	**Frequency**	**Frequency**	**Frequency**	**Frequency**	**Frequency**
Infections and infestations	Infection	Uncommon			Uncommon	Not known
	Rhinitis		Uncommon		Uncommon	
	URTI			Uncommon		
	Pyelonephritis	Uncommon				
	Furuncle	Uncommon				
	UTI				Common	Not known
	Vulvovaginal candidiasis		Uncommon		Common	
	Influenza		Uncommon		Common	
	Pharyngitis				Common	Not known

	Pneumonia					Not known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasm Skin cancer				Uncommon	 Not known
Blood and lymphatic system disorder	Leukopenia Anaemia Lymphadenopathy Coagulopathy			Uncommon	 Uncommon Uncommon	 Not known
Immune system disorders	Anaphylactic reaction					Not known
Endocrine disorders	Goiter Thyroiditis Pituitary apoplexy Hyperandrogenism	 Common			 Common 	Not known Not known
Metabolism and nutrition disorders	Anorexia Diabetes mellitus Increased appetite Decreased appetite Hypoglycemia Dehydration Hyperlipidaemia Hypercholesterolaemia Hyperphosphataemia Hypoproteinaemia Abnormal weight gain Abnormal loss of weight	Uncommon Uncommon Common Very common Common	 Uncommon Common Common	Uncommon Very common Common Very common Very common	 Common Very common Common	 Not known Not known Not known Not known Not known Not known Not known
Psychiatric disorders	Affect lability Mood swings[a] Personality disorder Nervousness Libido decreased Libido increased Insomnia Sleep disorder Depression[a] Major depression Anxiety Delusion Thinking abnormal Confusional state Euphoric mood Hostility Apathy Agitation Nervousness/anxiety Screaming Suicidal ideation Suicide attempt	Very common Uncommon Very common Very common Very common Very common Common Common Uncommon Uncommon Uncommon Common Uncommon Very common 	Common Common Common Common Common Uncommon 	 Very common Very common Very common Common Very common 	Very common Very common Common Very common Very common Common Common Common Uncommon Uncommon Common Uncommon 	 Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known
Nervous system disorders	Dizziness Dizziness postural Headache Paraesthesia Lethargy Somnolence Memory impairment Amnesia Dysgeusia Hypoaesthesia Syncope Migraine Hypertonia Ataxia Tremor Coordination abnormal Hyperkinesia Neuropathy peripheral Cerebrovascular accident Loss of consciousness TIA Paralysis Neuromyopathy Convulsion	Very common Very common Common Uncommon Uncommon Uncommon Common Uncommon 	Common Very common Common Uncommon Uncommon Common 	Very common Common Very common Common Common Common Common Common 	Common Very common Common Common Common Uncommon Common Common Very common Common Common Common Common 	Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known Not known
Eye disorders	Vision blurred Eye disorder Visual impairment Amblyopia Eye pain Conjunctivitis	 Uncommon Common Common Uncommon 	 Uncommon	 Common	 Common 	Not known Not known Not known Not known

	Dry eye					Not known
Ear and labyrinth disorders	Ear pain				Uncommon	
	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 infarction					Not known
	Angina pectoris					Not known
	Tachycardia	Uncommon	Uncommon		Common	Not known
	Palpitations	Common		Common	Common	
	Bradycardia					Not known
Vascular disorders	Hot flush			Very common		
	Vasodilatation	Very common	Very common		Very common	
	Lymphoedema					Not known
	Hypertension				Common	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			Uncommon	
	Sputum increased			Common		
	Cough			Common		Not known
	Laryngospasm				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	Uncommon	Common	Common	Not known
	Nausea	Very common	Common	Very common	Very common	Not known
	Vomiting		Uncommon	Common	Common	Not known
	Nausea and vomiting	Common	Uncommon		Common	
	Gastrointestinal hemorrhage					Not known
	Abdominal distention	Uncommon		Common	Common	Not known
	Diarrhoea	Common	Common	Common	Common	Not known
	Dysphagia					Not known
	Gingivitis			Common	Common	
	Dyspepsia	Uncommon			Common	
	Flatulence	Uncommon	Common		Common	
	Gastritis	Uncommon		Common		
	Gingival bleeding	Uncommon				
	Dry mouth	Common	Uncommon		Uncommon	Not known
	Abdominal pain	Common	Common		Common	
	Abdominal pain upper			Common		
	Abdominal pain lower			Common		
	Stomatitis			Common		
	Retching			Common		
	Melaena				Common	
	Colitis				Uncommon	
	Duodenal ulcer					Not known
	Gastrointestinal disorder					Not known
	Peptic ulcer					Not known
	Rectal polyp					Not known
Hepato-biliary disorders	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	Common	Not known
	Ecchymosis	Common			Common	Not known
	Acne	Very common		Common	Very common	
	Seborrhoea	Common				
	Rash	Common	Common	Common	Common	Not known
	Rash maculo-papular	Uncommon				
	Dry skin	Common	Common		Common	Not known
	Photosensitivity reaction	Uncommon				Not known

	Urticaria				Uncommon	Not known
	Skin odour abnormal		Uncommon			
	Hyperhidrosis	Common	Common	Very common	Very common	
	Dermatitis					Not known
	Hair growth abnormal					Not known
	Hirsutism	Common	Uncommon		Uncommon	
	Hair disorder	Uncommon			Common	
	Eczema			Common		
	Pruritus				Common	Not known
	Nail disorder		Uncommon		Common	
	Skin discolouration		Uncommon		Uncommon	
	Skin disorder				Uncommon	
	Skin nodule				Common	
	Dermatitis bullous		Uncommon			
	Pigmentation disorder					Not known
	Skin lesion					Not known
	Skin reaction	Very common	Common			
Musculoskeletal and connective tissue disorders	Bone pain			Common		
	Myalgia	Uncommon	Uncommon		Common	Not known
	Bone swelling					Not known
	Arthropathy	Common	Common		Common	Not known
	Arthralgia	Common	Common	Very common	Common	Not known
	Back pain	Common	Common	Very common	Common	
	Osteoarthritis			Common		
	Arthritis	Uncommon				
	Nuchal rigidity	Common			Uncommon	
	Neck pain	Common		Common	Uncommon	
	Muscular weakness			Common		
	Musculoskeletal stiffness			Common		
	Muscle twitching			Common	Uncommon	
	Muscle spasms				Common	
	Ankylosing spondylitis					Not known
	Tenosynovitis					Not known
Renal and urinary disorders	Urinary incontinence	Uncommon				Not known
	Dysuria	Common			Uncommon	
	Pollakiuria	Uncommon		Common		Not known
	Micturition urgency					Not known
	Haematuria					Not known
	Renal pain				Common	
	Bladder spasm					Not known
	Urinary tract disorder					Not known
	Urinary tract obstruction					Not known
Reproductive system and breast disorders	Breast tenderness					Not known
	Vaginal haemorrhage				Uncommon	Not known
	Dysmenorrhea				Common	
	Menstrual disorder		Uncommon			Not known
	Breast enlargement	Uncommon			Common	
	Breast engorgement	Uncommon				
	Breast atrophy	Common			Common	
	Genital discharge	Common				
	Vaginal discharge			Common		
	Galactorrhoea	Uncommon			Common	
	Breast pain	Common	Common	Common	Very common	Not known
	Pelvic pain	Common	Uncommon		Common	
	Metrorrhagia		Uncommon	Common	Uncommon	Not known
	Menopausal symptoms			Common		
	Dyspareunia				Common	
	Uterine disorder				Uncommon	
	Vulvovaginitis	Very common	Very common	Common	Very common	
	Menorrhagia		Uncommon			
General disorders and administration site conditions	Pain	Common	Common		Very common	Not known
	Chest pain	Common	Uncommon	Common	Common	
	Oedema	Common	Uncommon	Common		Not known
	Oedema peripheral	Common	Common	Common	Common	
	Face oedema	Uncommon				
	Generalised oedema	Uncommon			Common	
	Asthenia	Common	Common	Very common	Very common	Not known
	Fatigue			Common		
	Pyrexia			Common	Common	Not known
	Injection site reaction	Uncommon		Common	Common	Not known
	Injection site inflammation					Not known
	Injection site mass	Uncommon	Uncommon			
	Injection site pain	Common	Common	Very common	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 haematoma					Not known

	Chills	Common	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	Common	
	Condition aggravated		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
	Blood Ca increased					Not known
	Body temperature increased			Uncommon		
	Occult blood positive			Common		
	ECG abnormal					Not known
	ECG signs of myocardial ischemia					Not known
	LFT abnormal		Common			Not known
	Platelet count decreased					Not known
	Blood K decreased					Not known
	WBC count increased					Not known
	WBC count decreased					Not known
	PT prolonged					Not known
	APTT prolonged					Not known
	Laboratory test abnormal		Uncommon			
	Cardiac murmur					Not known
	LDL increased					Not known
	Blood TG increased					Not known
	Blood bilirubin increased					Not known
Injury, poisoning and procedural complications	Procedural pain			Common		
	Spinal fracture					Not known

[a] Depression and mood swing are commonly observed adverse reactions with long term use of GnRH agonists.

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose of leuprorelin acetate depot suspension. In animal studies, doses of 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.

*** 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.

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 of gonadotropins, chronic administration of leuprorelin acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble 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.

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.

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 – 3 month 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 steady-state 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 depot for 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 hepatic- and renal-impaired patients has not been determined.

PRE-CLINICAL SAFETY DATA
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/day). Also, in rat there was a significant but not a 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/day 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.

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

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

Once reconstituted with the sterile diluent, the suspension should be administered immediately. However, the suspension is considered stable for up to 24 hours at 25°C. Protect from light.

HOW SUPPLIED
Leuprorelin acetate for depot suspension is available in a single dose administration kit containing a pre-filled dual chamber syringe, a plunger and an alcohol wipe. The front chamber of the syringe contains sterile lyophilized microspheres, which are leuprorelin acetate incorporated in a biodegradable polymer of polylactic acid and the rear chamber contains a clear and colourless diluent.

Manufactured in Japan by:
Takeda Pharmaceutical Company Limited

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