

Data Sheet

Lucrin[®] Depot 3.75mg, 11.25mg and 30mg Prefilled Dual Chamber Syringe (PDS) Injection

Name of the Medicine

Non-proprietary Name

Leuprorelin (leuprolide) acetate

Description

Lucrin Depot PDS is a formulation of leuprorelin acetate supplied as sterile lyophilised microspheres which, when mixed with the accompanying diluent, forms a suspension.

Lucrin Depot contains either 3.75 mg, 11.25 mg or 30 mg of leuprorelin acetate per single dose. Lucrin Depot also contains carmellose sodium, gelatin (3.75mg only), mannitol, polysorbate 80, water for injection, acetic acid (11.25 mg and 30 mg only), PLGA (3.75 mg only), polylactic acid (11.25 mg and 30mg only).

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 causes inhibition of the growth of certain hormone dependent tumours (prostatic tumours in Nobel 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 and sex steroids. In males, testosterone is reduced to castrate or prepubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating medicine therapy at recommended doses.

Prostatic Cancer

The growth and function of the prostate gland is dependent upon the male hormone, testosterone. Treatment of prostatic carcinoma is aimed at achieving a testosterone blockage (chemical castration). Continuous administration of leuprorelin acetate in males results in a decrease of testosterone to castrate or prepubertal levels. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Gynaecological Use

Since oestrogen stimulates the growth of both uterine and endometrial tissue, the treatment of uterine fibroids and endometriosis with leuprorelin acetate is based on suppression of oestrogen production.

Uterine Fibroids

Leiomyoma uteri (uterine fibroids) is a gynaecological disorder characterised by the presence of benign tumours of myometrial origin, for which oestrogen usually functions as a growth-promoting factor. The effect of oestrogen depletion on the leiomyoma results in shrinkage of the fibroids and in alleviation of the symptoms, including menorrhagia and pelvic pain, pressure and discomfort. Improvement in haemoglobin and haematocrit has been noted following reduction or elimination of menorrhagia.

Endometriosis

The etiology of endometriosis is unclear, but several theories exist regarding its origin. The most probable cause is retrograde menstruation, but other possible sources included surgical transplantation and direct extension of the endometrium. Medical therapy in endometriosis is based on suppression of oestrogen production. The hypo-oestrogenic state resulting from the administration of Lucrin Depot produced atrophic changes in both uterine and ectopic endometrial tissue. This process included abatement of current endometrial implants, prohibition of new lesions, and possible reduction of adhesions, all of which can result in decreased pain and symptoms. In clinical trials, the majority of women experienced improvement in one or more of the signs and symptoms of endometriosis.

Suppression of pituitary gonadotropins usually results in elimination of the menstrual cycle. In conjunction with a 6-month course of therapy, following the last 28-day therapeutic period, the median time to resumption of menses was 52 days (range 7 to 183) in the uterine fibroids clinical studies and 51 days (range 9 to 142) in the endometriosis studies.

Since both oestrogen and androgen steroidogenesis are suppressed, the androgenic effects seen with other therapies are avoided.

Central Precocious Puberty (CPP)

Central Precocious Puberty (CPP) is a rare condition defined as the appearance of any signs of secondary sexual development before the age of 8 in females and 9 in males. Central precocious puberty is caused by the premature activation of the hypothalamic-pituitary-gonadal axis in the same pattern as occurs at puberty.

In children with central precocious puberty (CPP), stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and oestradiol are reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuporelin acetate.

The following physiologic effects have been noted with the chronic administration of leuporelin acetate in this patient population.

1. **Skeletal Growth.** A measurable increase in body length can be noted since the epiphyseal plates will not close prematurely.
2. **Organ Growth.** Reproductive organs will return to a prepubertal state.
3. **Menses.** Menses, if present, will cease.

In a study of 22 children with central precocious puberty, doses of Leuporelin Acetate for Depot Suspension were given every four weeks and plasma levels were determined according to weight categories as summarised in the following table:

Patient Weight Range (kg)	Group Weight Average (kg)	Dose (mg)	Trough Plasma Leuporelin Level Mean \pm SD (ng/mL)*
20.2 - 27.0	22.7	7.5	0.77 \pm 0.33
28.4 - 36.8	32.5	11.25	1.25 \pm 0.06
39.3 - 57.5	44.2	15	1.59 \pm 0.65

* Group average values determined at Week 4 immediately prior to leuporelin acetate injection. Medicine levels at 12 and 24 weeks were similar to respective 4 week levels.

Pharmacokinetics

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

Absorption

Following the administration of a 7.5mg of leuporelin acetate for depot suspension injection to adult patients, mean peak leuporelin plasma concentration was almost 20ng/mL at four hours and then declined to 0.36ng/mL at four weeks. However, intact leuporelin and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Nondetectable leuporelin plasma concentrations have been observed during chronic leuporelin acetate for depot suspension 7.5mg administration, but testosterone levels appear to be maintained at castrate levels.

Serum levels of leuporelin acetate 3.75mg were measured in 11 patients with pre-menopausal breast cancer over 12 weeks. Mean leuporelin acetate levels were above 0.1ng/mL after four weeks and remained stable after re-injection (at 8 and 12 weeks). There was no tendency for drug accumulation.

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

Following a single injection of the 3 - month formulation of leuporelin acetate depot suspension – 3 month 11.25mg in female subjects, a mean plasma leuporelin concentration of 36.3ng/mL was observed at 4 hours. Leuporelin 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) leuporelin concentration from 3 to 12 weeks was 0.23+0.09ng/mL. However, intact leuporelin 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.

Leuporelin acetate is continuously released from the lactic acid polymer for a period of 6 months after injection of Lucrin Depot 30mg PDS Injection. The carrier polymer is absorbed over time in a similar fashion to surgical suture material.

After single s.c. injection of Lucrin Depot 30mg PDS Injection 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.

Distribution

The mean steady-state volume of 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%.

Metabolism

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

Animal studies have shown ¹⁴C-labelled leuprorelin was metabolised into smaller inactive peptides which may be further catabolised.

The major metabolite (M-1) plasma concentrations measured in five prostate cancer patients reached maximum concentration two to six hours after dosing and were approximately 6% of the peak parent medicine concentration. One week after dosing, mean plasma M-1 concentrations were approximately 20% of mean leuprorelin concentrations.

Excretion

Following administration of leuprorelin acetate for depot suspension 3.75mg to three patients, less than 5% of the dose was recovered as parent and M-1 metabolite in the urine over 27 days.

Special Populations

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

Indications

Prostate Cancer

Lucrin Depot 3.75mg, 11.25mg and 30mg are indicated:

- in metastatic prostate cancer
- in locally advanced prostate cancer, as an alternative to surgical castration
- as an adjuvant treatment to radiotherapy in patients with high-risk localized or locally advanced prostate cancer
- as an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression

In clinical trials, the safety and efficacy of Lucrin Depot does not differ from that of the daily subcutaneous injection dosage.

Uterine Fibroids

Lucrin Depot 3.75mg and 11.25mg are indicated in the treatment of leiomyoma uteri (uterine fibroids) for a period of 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.

Endometriosis

Lucrin Depot 3.75mg and 11.25mg are indicated in the treatment of endometriosis for a period of 6 months. It can be used as sole therapy or as an adjunct to surgery.

Central Precocious Puberty

Lucrin Depot 3.75mg is indicated in the treatment of children with central precocious puberty (CPP). Children should be selected using the following criteria:

1. Clinical diagnosis of CPP (idiopathic or neurogenic) with onset of secondary sexual characteristics earlier than eight years in females and nine years in males.
2. Clinical diagnosis should be confirmed prior to initiation of therapy:
 - Confirmation of diagnosis of a pubertal response to a GnRH stimulation test. The sensitivity and methodology of this assay must be understood.
 - Bone age advanced one year beyond the chronological age.
3. Baseline evaluation should also include:
 - Height and weight measurements
 - Sex steroid levels
 - Adrenal steroid level to exclude congenital adrenal hyperplasia
 - Beta human chorionic gonadotropin level to rule out a chorionic gonadotropin secreting tumour
 - Pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumour
 - Computerised tomography of the head to rule out intracranial tumour

Breast Cancer

Lucrin Depot PDS 3.75mg and 11.25mg are indicated for the treatment of breast cancer in pre- and peri-menopausal women in which hormone therapy is specified.

Contraindications

Lucrin Depot is contraindicated in patients with known hypersensitivity to leuprorelin acetate or similar nonapeptides or to any of the inactive components. Isolated cases of anaphylaxis have been reported.

In case hormone-independence of the carcinoma has been demonstrated, treatment with Lucrin Depot 30mg PDS Injection is not indicated.

After surgical castration, Lucrin Depot 30mg PDS Injection does not offer further reduction of testosterone levels.

Lucrin Depot is contraindicated in women who are or may become pregnant while receiving treatment with this medicine. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024 and 0.024mg/kg (1/600 to 1/6 the adult dose, 1/1200 to 1/12 of the human paediatric dose) to rabbits, Lucrin Depot produced a dose related increase in major foetal abnormalities. Similar studies in rats failed to demonstrate an increase in foetal malformations. There was increased foetal mortality and decreased foetal weights with the two higher doses of Lucrin Depot in rabbits and with the highest dose (0.024mg/kg) in rats.

The effects on foetal mortality are logical consequences of the alterations in hormonal levels brought about by this medicine. Therefore, a possibility exists that spontaneous abortion may occur if the medicine is administered during pregnancy.

Lucrin Depot is also contraindicated in women during breastfeeding.

Lucrin Depot should not be administered to patients with undiagnosed vaginal bleeding.

Precautions

Prostate Cancer

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogues. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily leuporelin 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 obstruction should be closely observed during the first few weeks of therapy.

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

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 use of GnRH agonists in men. The risk appears to be 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 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.

Gynaecological Use

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the medicine. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these 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.

Since loss of bone density can be anticipated as part of the natural menopause, it may also be expected to occur during a medically induced hypo-oestrogenic state. Bone loss has been found to be reversible after completion of a six month course of leuporelin acetate.

Repeat courses of leuporelin acetate or any other GnRH agonist following an initial six month course of therapy should not be considered without assessment of the risk of developing osteoporosis. No data are available for women receiving the treatment for a longer period of time.

Central Precocious Puberty

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

Non-compliance with medicine regimen or inadequate dosing may result in inadequate control of the pubertal process. The consequences of poor control include the return of pubertal signs such as menses, breast development, and testicular growth. The long-term consequences of inadequate control of gonadal steroid secretion are unknown, but may include a further compromise of adult stature.

General

Convulsions

Postmarketing reports of convulsions have been observed in patients on leuporelin acetate therapy. These included patients in the female and paediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above

Effects on Fertility

Clinical and pharmacological studies with leuporelin acetate and similar analogues have shown full reversibility of fertility suppression when the therapy is discontinued after continuous administration for periods of up to 24 weeks.

Use in Pregnancy

Category C (see Contraindications)

The safe use of leuporelin acetate in pregnancy has not been established clinically. Before starting treatment with leuporelin acetate, it is advisable to establish whether the patient is pregnant. Leuporelin is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used.

Use in Lactation (see Contraindications)

It is not known whether leuporelin acetate is excreted in human milk; therefore Lucrin Depot should not be used by nursing mothers.

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 medicine was administered subcutaneously at high daily doses (0.6 to 4mg/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 leuporelin acetate-induced tumours or pituitary abnormalities were observed at a dose as high as 60mg/kg for two years. Patients have been treated with leuporelin acetate for up to three years with doses as high as 10mg/day and for two years with doses as high as 20mg/day without demonstrable pituitary abnormalities.

Genotoxicity

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

Interactions with other Medicines

No pharmacokinetic-based medicine-medicine interaction studies have been conducted with leuporelin acetate depot suspension. However, because leuporelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the medicine is only about 46% bound to plasma proteins, medicine interactions would not be expected to occur.

Administration of leuporelin acetate depot in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after leuporelin 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 leuporelin acetate depot may be misleading.

Effect on Laboratory Tests

Prostate Cancer

Response to leuporelin acetate should be monitored by measuring serum levels of testosterone, as well as prostate specific antigen and 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. 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 occur early in treatment. However, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline.

Central Precocious Puberty

Response to leuporelin 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 prepubertal levels if the dose is inadequate (see Precautions). Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to prepubertal levels.

Effect on ability to drive and use machinery

There are no reported effects on the ability to drive or operate machinery. However, as with all medicines care should be taken until the individual effects of Lucrin Depot are known.

Adverse Effects

Adverse effects reported in clinical trials and post or part of marketing surveillance for each respective indication are included below.

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 haematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms (see Precautions).

In a clinical trial of Lucrin Depot, the following adverse reactions were reported to have a possible or probable relationship to the medicine as ascribed by the treating physician in 5% or more of the patients receiving the medicine. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not medicine related are excluded.

	Leuprorelin Acetate for Depot Suspension 3.75mg and 11.25mg	
	N=56	(%)
Cardiovascular System		
Oedema	7	(12.5)
Gastrointestinal System		
Nausea/vomiting	3	(5.4)
Endocrine System		
Decreased Testicular Size*	3	(5.4)
Hot Flushes/sweats*	33	(58.9)
Impotence*	3	(5.4)
Central/Peripheral Nervous System		
General Pain	4	(7.1)
Respiratory System		
Dyspnoea	3	(5.4)
Miscellaneous		
Asthenia	3	(5.4)
* Physiologic effect of decreased testosterone		

In this same study, the following adverse reactions were reported in less than 5% of the patients on Lucrin Depot:

Cardiovascular System: angina, cardiac arrhythmia;

Gastrointestinal System - anorexia, diarrhoea,

Endocrine System - gynaecomastia, libido decrease;

Musculoskeletal System - bone pain, myalgia;

Central/Peripheral Nervous System - paraesthesia, insomnia;

Respiratory System - haemoptysis;

Integumentary System - dermatitis, local skin reactions, hair growth;

Urogenital System - dysuria, frequency/urgency, haematuria, testicular pain;

Miscellaneous - diabetes, fever/chills, hard nodule in throat, increased calcium, weight gain, increased uric acid.

Lucrin Depot 30mg

Administration of Lucrin Depot 30mg regularly leads to an initial short-term increase in the serum level of testosterone, potentially resulting in a transient exacerbation of certain disease symptoms (onset or exacerbation of bone pain, urinary tract obstruction and its consequences, bone marrow suppression, myasthenia of the leg, and lymphoedema). This exacerbation of symptoms usually subsides spontaneously on continued therapy with Lucrin Depot 30mg, without leading to the need to discontinue Lucrin Depot 30mg.

Due to suppression of sex hormones adverse reactions may be observed. Their incidences are defined as follows: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1.000, <1/100), rare (> 1/10.000, < 1/1.000), very rare (< 1/10.000).

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Uncommon	general allergic reactions (i.e., fever, pruritus, eosinophilia, and skin rash)
Metabolism and nutrition disorders	Common	loss of appetite
	Rare	alterations in diabetic metabolic state (increase or decrease in plasma glucose levels)
Psychiatric disorders	Common	depression, which may also occur due to underlying disease
Nervous system disorders	Common	headache
	Rare	dizziness transient alterations of taste
	Very rare	like with other medicinal products from this substance class there are very rare reports of pituitary apoplexy after initial administration of leuporelin in patients with pituitary adenoma.
	Not known	Convulsion
Vascular disorders	Very common	hot flushes
	Rare	alterations in blood pressure (hypertension or hypotension)
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea
Skin and subcutaneous tissue disorders:	Uncommon	dry skin and/or mucosa
	Rare	Alopecia
Musculoskeletal, connective tissue and bone disorders:	Very common	bone pain
	Common	joint or back pain, muscle weakness
Reproductive system and breast disorders	Very common	decrease in or loss of libido and potency, reduction in testicle size
	Common	Gynaecomastia

System Organ Class	Frequency	Adverse Reaction
	Uncommon	testicular pain
Renal and urinary disorders	Very common	Nocturia Dysuria
General disorders and administration site conditions	Very common	reactions at the injection site, e.g., erythema, injection site pain, edema, pruritus, which generally abate with continued. In single cases abscesses were observed. In case of rarely occurring abscesses testosterone levels should be monitored, as a possible elevation of testosterone may result from inadequate leuprorelin absorption from the depot. Increased sweating
	Common	Fatigue peripheral oedema paraesthesia sleep disturbances

Further observations:

Very common: weight gain

Uncommon: weight loss

Alterations in laboratory parameters:

Common: elevations of LDH, transaminases, gamma-GT and alkaline phosphatase which, however, can be a symptom of the underlying disease.

Response to Lucrin Depot 30mg PDS Injection can be verified by monitoring serum testosterone, acid phosphatase, and PSA (prostate-specific antigen) levels. Specifically, there occurs an initial temporary rise in the testosterone level at the start of treatment, followed by a decrease within a period of two weeks. After two to four weeks testosterone levels are reached similar to those observed after bilateral orchiectomy and persisting in the castration range throughout the entire treatment period.

In the initial phase of therapy with Lucrin Depot 30mg PDS Injection, a transient rise in acid phosphatase may occur. However, acid phosphatase values usually return to normal or near-normal within a few weeks.

The resulting hypogonadism, commonly observed under long-term therapy with GnRH analogues or orchiectomy, may lead to the onset of osteoporosis, with the increased risk for bone fracture (see Precautions). In patients at risk, the additional administration of a bisphosphonate may prevent such bone demineralization.

Gynaecological Use

Oestradiol levels may increase during the first weeks following the initial injection, but then decline to baseline levels. This transient increase in oestradiol can be associated with a temporary worsening of signs and symptoms (see **Precautions**).

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke and transient ischaemic 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 agonists and these events.

Endometriosis

In two clinical trials treating endometriosis, one comparing leuprorelin acetate for depot suspension with danazol and the other with placebo, the following adverse reactions were reported to have a possible or probable relationship to study medicines as ascribed by the treating physician in 5% or more of the patients receiving the medicine. Reaction considered not medicine related are excluded.

	Leuprorelin Acetate for Depot Suspension		Danazol		Placebo	
	N=166	(%)***	N=136	(%)**	N=31	(%)
Cardiovascular System						
Oedema	12	(7)	17	(13)	1	(3)
Gastrointestinal System						
Nausea/vomiting	21	(13)	17	(13)	1	(3)
GI disturbances*	11	(7)	8	(6)	1	(3)
Endocrine System						
Hot Flushes/sweats*	139	(84)	77	(57)	9	(29)
Breast changes, tenderness/pain*	10	(6)	12	(9)	0	(0)
Decreased Libido*	19	(11)	6	(4)	0	(0)
Androgen-like effects	22	(13)	44	(32)**	1	(3)
Virilism	0	(0)	1	(1)	0	(0)
Acne	17	(10)	27	(20)	0	(0)
Seborrhoea	2	(1)	5	(4)	0	(0)
Hirsutism	2	(1)	9	(7)	1	(3)
Voice alteration	1	(1)	2	(1)	0	(0)
Musculoskeletal System						
Myalgia*	1	(1)	7	(5)	0	(0)
Joint Disorder*	14	(8)	11	(8)	0	(0)
Central/Peripheral Nervous System						
Depression/emotional liability*	36	(22)	27	(20)	1	(3)
Headaches*	53	(32)	30	(22)	2	(6)
Dizziness	19	(11)	4	(3)	0	(0)
Insomnia/sleep disorders*	2	(1)	4	(3)	0	(0)
General pain	31	(19)	22	(16)	1	(3)
Neuromuscular disorders*	11	(7)	17	(13)	0	(0)
Nervousness*	8	(5)	11	(8)	0	(0)
Paraesthesias	12	(7)	11	(8)	0	(0)

	Leuprorelin Acetate for Depot Suspension		Danazol		Placebo	
	N=166	(%)***	N=136	(%)**	N=31	(%)
Integumentary System						
Skin reactions	17	(10)	20	(15)	1	(3)
Urogenital System						
Vaginitis*	46	(28)	23	(17)	0	(0)
Miscellaneous						
Asthenia	5	(3)	9	(7)	0	(0)
Weight gain/loss	22	(13)	36	(26)	0	(0)
* Physiologic effect of decreased oestrogen						
** Individual Percentages equal 33% due to rounding						
*** Data combined from both studies						

Laboratory: As anticipated, when inducing a transient therapeutic menopausal state, changes in the HDL/LDL ratios were observed in both treatment groups, but the clinical implication of these changes in this patient population for a restricted therapeutic period is unclear.

Isolated elevations of SGOT were observed in both leuprorelin acetate for depot suspension and danazol-treated patients.

In these same studies, the following were reported in less than 5% of patients receiving leuprorelin acetate for depot suspension:

Cardiovascular System - Palpitations, Syncope, Tachycardia

Gastrointestinal System - Dry mouth, Thirst, Appetite changes

Central/Peripheral Nervous System - Anxiety, Personality disorder, Memory disorder, Delusions

Integumentary System - Ecchymosis, Alopecia, Hair disorder

Urogenital System - Dysuria, Lactation

Miscellaneous - Ophthalmologic disorders, Lymphadenopathy

Uterine Fibroids

In three clinical trials of treating uterine fibroids, the following adverse reactions were reported to have a possible or probable relationship to Lucrin Depot as ascribed by the treating physician in 5% or more of the patients receiving the medicine. Reactions considered not related are excluded.

	Leuprorelin Acetate for Depot Suspension		Placebo	
	N=63	(%)	N=65	(%)
Cardiovascular System				
Oedema	7	(11.1)	1	(1.5)
Gastrointestinal System				
Nausea/vomiting	5	(7.9)	2	(3.0)
Endocrine System				

	Leuprorelin Acetate for Depot Suspension		Placebo	
	N=63	(%)	N=65	(%)
Hot flushes/sweats*	52	(82.5)	5	(7.7)
Musculoskeletal System				
Joint disorder	9	(14.3)	0	(0)
Central/Peripheral Nervous System				
Headache*	16	(25.4)	6	(9.2)
Depression/emotional lability	8	(12.7)	2	(3.1)
Insomnia	6	(9.5)	0	(0)
Dizziness	0	(0)	3	(4.6)
General Pain	5	(7.9)	0	(0)
Integumentary System				
Local skin reactions	5	(7.9)	0	(0)
Urogenital System				
Vaginitis*	9	(14.3)	0	(0)
Miscellaneous				
Asthenia	8	(12.7)	2	(3.0)
* Physiologic effect of decreased oestrogen				

In these same studies, the following were reported in less than 5% of patients receiving Lucrin Depot:

Gastrointestinal System - constipation, diarrhoea, dry mouth, increased appetite, flatulence

Endocrine System - decreased libido, breast pain

Musculoskeletal System - myalgia, hypertonia

Central/Peripheral Nervous System - nervousness, paraesthesia

Integumentary System - nail disorder

Miscellaneous - weight gain/loss, taste disorder, flu syndrome, vaginal odour

Breast Cancer

In a comparative study for leuprolide acetate, premenopausal breast cancer patients were treated with Leuprolide Acetate for Depot Suspension 11.25mg and Leuprolide Acetate 3.75mg as well as tamoxifen. The following are most common adverse events that were considered at least possibly related to leuprolide for at least 10% of patients.

Most common adverse events, Safety Population (Study CPH-101)

Adverse Event	Leuprolide acetate 3.75mg N = 71	Leuprolide acetate 11.25mg N = 71
Any adverse event	70 (98.6%)	69 (97.2%)
Feeling of warmth	51 (71.8%)	50 (70.4%)
Headache dull	30 (42.3%)	18 (25.4%)
Common cold syndrome	19 (26.8%)	20 (28.2%)
Nausea	15 (21.1%)	12 (16.9%)

Adverse Event	Leuprolide acetate 3.75mg N = 71	Leuprolide acetate 11.25mg N = 71
Dermatitis	12 (16.9%)	14 (19.7%)
Headache	12 (16.9%)	12 (16.9%)
Diaphoresis	12 (16.9%)	9 (12.7%)
Dizziness	9 (12.7%)	6 (8.5%)
Injection site induration	8 (11.3%)	22 (31.0%)
Injection site pain	8 (11.3%)	9 (12.7%)
Fever	4 (5.6%)	8 (11.3%)

Source Data: Study Report CPH-101 Table 3.3.1.4-8

In a pivotal clinical study comparing Leuprolide Acetate for Depot Suspension 11.25mg to CMF-chemotherapy in pre- and peri-menopausal breast cancer patients, the following adverse events were reported for at least 10% of patients in either treatment group.

Most common adverse events, Safety Population (Study B02/EC 008)

	Leuprolide acetate 11.25mg N = 294		CMF N = 295	
	n	%	n	%
Any adverse event	287	97.6	294	99.7
Weight increase	236	80.3	170	57.6
Sweating increased	235	79.9	157	53.2
Hot flushes	249	84.7	130	44.1
Decrease in physical ability	115	39.1	221	74.9
Nausea	33	11.2	272	92.2
Weight decrease	115	39.1	148	50.2
Weakness generalised	52	17.7	189	64.1
Appetite decreased	26	8.8	211	71.5
Vomiting	12	4.1	205	69.5
Headache	85	28.9	94	31.9
Nervousness	83	28.2	71	24.1
Appetite increased	98	33.3	43	14.6
Mood swings	75	25.5	65	22.0
Alopecia	5	1.7	124	42.0
Back pain	63	21.4	52	17.6
Sleeplessness	64	21.8	51	17.3
Dizziness	52	17.7	54	18.3
Hair loss	22	7.5	65	22.0
Diarrhoea	13	4.4	70	23.7
Arthralgia	54	18.4	25	8.5
Depression	42	14.3	36	12.2
Cervical pain	44	15.0	26	8.8
Appetite lost	3	1.0	65	22.0

	Leuprolide acetate 11.25mg N = 294		CMF N = 295	
Leucopenia	3	1.0	54	18.3
Joint pain	37	12.6	19	6.4
Erythema	21	7.1	33	11.2
Constipation	15	5.1	34	11.5
Vaginitis	34	11.6	15	5.1

Source Data: Study Report B02/EC 008, Table 67

Central Precocious Puberty

Potential exacerbations of signs and symptoms during the first few weeks of treatment (see Warnings and Precautions) is a concern in patients with rapidly advancing central precocious puberty.

In two studies of children with central precocious puberty, in 2% or more of the patients receiving the medicine, the following adverse reactions were reported to have a possible or probable relationship to medicine as ascribed by the treating physician. Reactions considered not medicine related are excluded.

	Leuprorelin Acetate for Depot Suspension	
	N = 421	Percent (%)
Body as a Whole		
General Pain	12	(3)
Headache	11	(3)
Injection Site Reaction Including Abscess*	37	(9)
Integumentary System		
Acne/Seborrhoea	13	(3)
Rash Including Erythema Multiforme	12	(3)
Nervous System		
Emotional Lability	19	(5)
Urogenital System		
Vaginitis/ Vaginal Bleeding/ Vaginal Discharge	13	(3)

* Most events were mild or moderate in severity

In those same studies, the following adverse reactions were reported in less than 2% of the patients:

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

Cardiovascular System – bradycardia, hypertension, peripheral vascular disorder, syncope

Gastrointestinal System – constipation, dyspepsia, dysphagia, gingivitis, increased appetite, nausea/vomiting

Endocrine System - accelerated sexual maturity, feminization

Haemic and Lymphatic System - purpura

Metabolic and Nutritional Disorders – growth retarded, peripheral oedema, weight gain;

Musculoskeletal System – arthralgia, joint disorder, myalgia, myopathy

Nervous System – depression, hyperkinesia, nervousness, somnolence;

Respiratory System – asthma, epistaxis, pharyngitis, rhinitis, sinusitis

Integumentary System - alopecia, hair disorder, hirsutism, leukoderma, nail disorder, skin hypertrophy

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

Laboratory

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

Postmarketing Surveillance - All Indications

The following adverse events have been observed with this or other formulations of leuprorelin acetate injection. As leuprorelin has multiple indications, and therefore patient populations, some of these adverse events may not be applicable to every patient. For a majority of these adverse events, a cause and effect relationship has not been established.

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

Cardiovascular: angina, bradycardia, cardiac arrhythmia, congestive heart failure, ECG changes/ischemia, hypertension, hypotension, murmur, myocardial infarction, phlebitis, pulmonary emboli, stroke, sudden cardiac death, syncope/blackouts, tachycardia, thrombosis, transient ischemic attack, varicose veins.

Digestive: constipation, diarrhoea, dry mouth, duodenal ulcer, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, increased appetite, liver function test abnormal, nausea, peptic ulcer, rectal polyps, thirst, vomiting.

Endocrine: diabetes, thyroid enlargement.

Haemic/Lymphic: anaemia, ecchymosis, lymphedema, PT increased, PTT increased, platelets decreased, WBC decreased, WBC increased.

Metabolic and Nutritional

BUN increased, calcium increased, creatinine increased, dehydration, oedema, hyperlipidemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphatemia, hypoglycemia, hypoproteinemia, potassium decreased, uric acid increased, bilirubin increased.

Musculoskeletal: ankylosing spondylosis, joint disorders, joint pain, myalgia, pelvic fibrosis, spinal fracture, paralysis, tenosynovitis-like symptoms.

Nervous: anxiety, convulsion, delusions, depression, dizziness, hypoesthesia, insomnia, lethargy, libido increased, lightheadedness, memory disorder, mood swings, nervousness, neuromuscular disorders, numbness, paraesthesia, peripheral neuropathy, sleep disorders

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

Skin and Appendages: Carcinoma of skin/ear, dermatitis, dry skin, hair growth, hair loss, hard nodule in throat, pigmentation, pruritus, rash, skin lesions, urticaria.

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

Urogenital: bladder spasms, breast pain, breast tenderness, gynecomastia, haematuria, incontinence, menstrual disorders including breakthrough and sustained vaginal bleeding, penile swelling, penis disorders, prostate pain, testicular atrophy, testicular pain, testicular size decreased, urinary disorders, urinary frequency, urinary obstruction, urinary tract infection, urinary urgency.

Isolated cases of anaphylaxis have been reported.

Injection site reactions including pain, 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.

Dosage and Administration

Lucrin Depot must be administered under the supervision of a physician.

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

Prostatic Cancer

The recommended dose of Lucrin Depot 3.75 mg one injection given intramuscularly or subcutaneously every month.

The recommended dose of Lucrin Depot 3 month 11.25 mg is one injection given intramuscularly or subcutaneously every three months

The recommended dose of Lucrin Depot 6 month 30 mg is one injection given intramuscularly or subcutaneously every six months.

Generally, the treatment of advanced, hormone-sensitive prostate cancer is continued on a long-term basis. In view of potential clinical signs of progression presenting despite adequate treatment, treatment with Lucrin Depot 30 mg should be monitored for success on a regular basis by means of clinical examinations as well as laboratory evaluations of prostate-specific antigen (PSA), and serum testosterone levels. The application interval should be 168 days to maximum 180 days (24 to 26 weeks) in order to avoid a renewed deterioration of symptoms. As animal experimental findings demonstrated, it is crucial to avoid accidental intra-arterial injection, in view of the potential onset of thrombosis of small vessels distal to the injection site.

Uterine Fibroids, Endometriosis or Breast Cancer

The recommended dose of Lucrin Depot 3.75 mg one injection given intramuscularly or subcutaneously every month.

The recommended dose of Lucrin Depot 3 month 11.25mg is one injection given intramuscularly or subcutaneously every three months

Use of Lucrin in treatment of benign gynaecological conditions should be limited to six months because of possible osteoporotic effects.

Central Precocious Puberty (3.75mg presentation only)

The dose of Lucrin Depot must be individualised for each child. The dose is based on a mg/kg ratio of medicine to body weight. Younger children require higher doses on a mg/kg ratio.

For each dosage, after one to two months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, sex steroids, and Tanner staging to confirm downregulation. Measurements of bone age for advancement should be monitored every 6 to 12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters.

The first dose found to result in adequate downregulation can probably be maintained for the duration of therapy in most children. However, there is insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate downregulation be verified in such patients whose weight has increased significantly while on therapy.

Discontinuation of Lucrin Depot should be considered before age 11 for females and age 12 for males.

Administration Guidelines - Central Precocious Puberty

Initial Dose

The recommended starting dose of Lucrin Depot is 0.3mg/kg (minimum 7.5mg), administered either intramuscularly or subcutaneously.

The starting dose is dictated by the child's weight, as follows:

Child's Weight	Actual Dosage	Number of Injection Sites	Total Dosage
≤ 25kg	3.75mg x 2	1	7.5mg
>25 - 37.5kg	3.75mg x 3	2	11.25mg
>37.5kg	3.75mg x 4	2	15mg

Note: When two injections are required to achieve the desired total dosage, they should be administered at the same time, two injections should however be administered at different injection sites.

Maintenance Dose

If total down-regulation is not achieved, the dose should be titrated upward in increments of 3.75mg every four weeks. This dose will be considered the maintenance dose.

Lucrin Depot Reconstitution

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

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

2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6-8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
3. Keep the syringe UPRIGHT. Gently mix the microspheres (particles) thoroughly to form a uniform suspension. The suspension will appear milky.
4. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
5. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
6. Inject the entire contents of the syringe intramuscularly or 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.

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

Stability Once Reconstituted

Although the solution has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately. As with other medicines administered by injection, the injection sites should be varied periodically.

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.

For advice on the management of overdose please contact the New Zealand Poisons Information Centre on 0800 764 766.

Presentation and Storage Conditions

Lucrin Depot PDS is available in a single dose pack of a dual chamber syringe containing sterile lyophilised microspheres of leuprorelin acetate in the front chamber and 1mL of diluent in the rear chamber.

When the contents of the chambers are mixed, Lucrin Depot 3.75mg PDS is administered as a single intramuscular or subcutaneous injection once a month, Lucrin Depot 11.25mg PDS is administered as a single intramuscular or subcutaneous injection once every three months and Lucrin Depot 30mg PDS is administered as a single intramuscular or subcutaneous injection once every six months.

Store below 25°C. Do not freeze. Protect from light.

Further Information

Information for Parents of Children Treated with Lucrin Depot for Central Precocious Puberty

Prior to starting therapy with Leuprorelin Acetate Depot Suspension, the parent or guardian must be aware of the importance of continuous therapy. Adherence to four week medicine administration schedules must be accepted if therapy is to be successful.

- During the first two months of therapy, a female may experienced menses or spotting. If bleeding continues beyond the second month, notify the physician.
- Any irritation at the injection site should be reported to the physician immediately.
- Report any unusual signs or symptoms to the physician.

Name and Address of the Sponsor

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Medicine Schedule

Prescription Medicine

Date of Preparation

June 2011

Version 01