

Data Sheet

Lucrin[®] 5mg/mL Injection

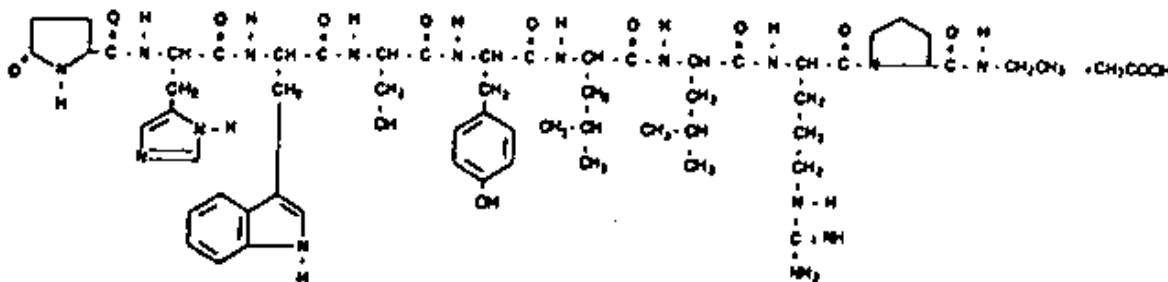
Name of the Medicine

Non-proprietary Name

Leuprorelin acetate

Chemical Structure

Leuprorelin acetate has the following structural formula:



CAS Number

74381-53-6

Description

Lucrin (leuprorelin acetate injection) is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analogue possesses greater potency than the natural hormone. Leuprorelin acts as an inhibitor of gonadotropin production and is chemically unrelated to the steroids. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tryosyl-D-leucyl-L-leucyl-L-arginyl-L-proline ethylamide monoacetate.

Lucrin is a sterile, aqueous solution intended for subcutaneous injection. Leuprorelin is not active when administered orally. It is available in multiple-dose vials containing 5mg/mL of leuprorelin acetate, sodium chloride for tonicity adjustment, 9mg/mL of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Pharmacology

Leuprorelin acts as a potent inhibitor of gonadotropin production. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprorelin results in suppression of ovarian and testicular steroidogenesis. No studies in animals or humans have yet established whether this effect is reversible upon discontinuation of drug therapy. Administration of leuprorelin has resulted in inhibition of tumour growth (prostatic tumours in Noble and Dunning male rats and DMBA-induced mammary tumours in female rats) as well as atrophy of the reproductive organs. An additional mechanism of action, a direct effect on the gonads by downregulation of the gonadotropin receptors, is suggested in some animal studies.

In humans, subcutaneous administration of single daily doses of leuprorelin results in an initial increase in circulating levels of luteinising 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 daily administration of leuprorelin results in decreased levels of LH and FSH in all patients. In males, androgens are reduced to castrate levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and are maintained as long as treatment continues.

In one study, bioavailability by subcutaneous administration was found to be comparable to intravenous administration. Leuporelin has a plasma half-life of approximately 3 hours. The metabolism, distribution and excretion of leuporelin in man have not been determined.

Assisted Reproduction:

As with other GnRH analogs, isolated cases of ovary hyperstimulation have been reported associated with the use of leuporelin with gonadotrophins. The possibility of occurrence and the ovary response to hyperovulation are very much related to the activity of endogenous gonadotrophins. The administration of leuporelin produces the pituitary suppression that allows for a better control of the LH values and thus increases the possibility of obtaining the endogenous gonadotrophin stimulation.

Indications

Prostate Cancer

Lucrin (leuporelin acetate) is 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

Assisted Reproductive Techniques

Lucrin is also indicated for controlled ovarian hyperstimulation for in-vitro fertilization or other assisted reproductive technique options.

Contraindications

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

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

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

Leuporelin acetate injection is contraindicated in patients with known hypersensitivity to leuprolide acetate or similar nonapeptides or any of the excipients.

Precautions

General: Isolated cases of short-term worsening of signs and symptoms have been reported during initiation of therapy. Patients with urinary tract obstruction should be closely observed during the first few weeks of treatment. Patients with metastatic vertebral lesions should begin leuporelin therapy under close supervision.

(See ADVERSE EFFECTS section)

Bone mineral density changes can occur during any hypoestrogenic state. Bone mineral density loss may be reversible after withdrawal of leuprorelin 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 the use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving GnRH agonists should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Effect on QT/QTc Interval

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

Convulsions

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

'Flare' Phenomenon: The initial increase in circulating levels of pituitary gonadotrophins and gonadal steroids leads in some patients to a transient exacerbation of symptoms and signs ('flare' phenomenon). The exacerbation may include worsened bone pain, ureteric obstruction and spinal cord compression. This possibility should be taken into account in deciding to initiate leuprorelin therapy in patients with existing obstructive uropathy or vertebral metastases. Early symptoms of spinal cord compression such as paraesthesiae should alert the physician to the need for intensive monitoring and possible treatment.

There is no information available on the clinical effects of interrupting leuprorelin therapy and whether this will produce a withdrawal 'flare'.

Effects on Fertility

Standard fertility and reproduction performance studies in animals cannot be conducted with leuprorelin because the compound affects the pituitary-gonadal axis and exerts an antifertility effect. Embryo-lethal effects were seen at 3-10 microgram/Kg in rats and at 0.1 microgram/Kg in rabbits.

Use in Pregnancy (Category D)

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

Use in Lactation

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

Paediatric Use

Safety and effectiveness in children have not been established.

Use in the Elderly

Carcinogenicity

Two year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related incidence of pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4mg/kg). This study also revealed an increased incidence of pancreatic islet cell adenomas, but their incidence showed a negative trend with dose, suggesting that it may not be drug-related. In mice, no pituitary abnormalities were observed at a dose as high as 60mg/kg for two years. In short term toxicity studies in mice treated for 3 months with 20-200 mg/kg, hypertrophic and castration cells were found in the anterior pituitary. Neither pituitary nor pancreatic changes were found in cynomolgus monkeys treated for 12 months with 10 mg/kg daily.

Genotoxicity

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

Effect on Laboratory Tests

Response to leuprorelin therapy may be monitored by measuring serum levels of testosterone as well as prostate-specific antigen and prostatic acid phosphatase. Clinical studies demonstrated the following: in the majority of non-orchietomised patients, testosterone levels increased during the first four days of treatment. They then decreased and by day 14 had returned to baseline levels or below. Castrate levels (defined as 0.25 ng/mL) were reached in 2 to 4 weeks. Once attained, castrate levels were maintained as long as drug administration continued. Transient increases in acid phosphatase levels sometimes occurred early in the treatment period; however, by the fourth week the elevated levels usually decreased to values at or near normal

The effects of leuprorelin on bone lesions may be monitored by bone scans while its effect on prostatic lesions may be monitored by ultrasonography and/or CT scan in addition to digital rectal examination.

Assisted Reproduction

The induction of ovulation in assisted reproduction techniques must be done under the supervision of a specialist in this area. In some women with predisposition especially women with polycystic ovary disease, the treatment may cause excessive follicular response. In case of ovary hyper stimulation, the gonadotrophin administration must be interrupted while continuing the treatment with leuprorelin acetate for a few days, to prevent the elevation of luteinizing hormone (LH). The response of the ovary to the combination of leuprorelin acetate and gonadotrophins administered at the same dose can vary from woman to woman and between cycles in the same woman.

Adverse Effects

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

In clinical studies, an initial rise in serum androgen levels usually occurred in non-orchietomised patients during the first 4 days of treatment. This was occasionally associated with a transient worsening of signs and symptoms, usually a mild increase in bone pain. In a few cases, a transient worsening of existing haematuria and urinary tract obstruction occurred during the first week. In each case, leuporelin administration was continued and the symptom subsided in one to two weeks. Transient weakness and parasthesia of the lower limbs have been reported in a few patients. The relationship of these observations to leuporelin administration is unknown. Nevertheless, the potential for exacerbation of signs and symptoms, particularly during the first few weeks of treatment, is a concern in patients with impending neurologic compromise and in patients with severe obstructive uropathy.

In a comparative clinical trial of Lucrin (1 mg/day) versus DES (3 mg/day), eighteen of the patients randomised to DES discontinued treatment because of adverse reactions. Only three patients randomised to leuporelin discontinued treatment for this reason. The administration of leuporelin is associated with a higher incidence of hot flashes, while the administration of DES is associated with a higher incidence of thromboembolic problems, oedema, nausea and vomiting, gynaecomastia, and breast tenderness. The following adverse reactions were reported by 3% or more of the patients on either drug.

	Lucrin (N=98)	DES (N=101)
	Number of Reports	
Cardiovascular		
Congestive heart failure	1	3
Oedema (peripheral)	8	23
Thrombophlebitis/Phlebitis/ Pulmonary emboli	1	7
Central Nervous System		
Anxiety	0	3
Dizziness	6	4
Pain	5	3
Headache	5	2
Paresthesia	3	0
Endocrine		
Gynaecomastia/breast tenderness	3	49
Hot flashes	51	11
Impotence	2	11
Gastrointestinal		
Anorexia	2	3
Constipation	3	1
Nausea/vomiting	5	16
Musculoskeletal		
Bone Pain	3	1

	Lucrin	DES
Muscle Spasms	0	3

In a non-comparative study using non-fasting blood glucose measurements, 51 of 72 patients with normal pre-study blood glucose levels subsequently had episodes of hyperglycaemia after commencement of treatment.

The following additional adverse reactions were reported in less than 3% of the patients in this study and their relationship to Lucrin is unknown:

Cardiovascular	- cardiac arrhythmias, myocardial infarction
Endocrine	- decreased testicular size
Gastrointestinal	- gastrointestinal bleeding
Haemic/Lymphatic	- decreased haematocrit and haemoglobin
Integumentary	- erythema and ecchymosis at the injection site, rash, hair loss, itching
Miscellaneous	- aesthenia, increased BUN and creatinine, fatigue, fever, facial swelling
Musculoskeletal	- myalgia
Nervous System	- blurred vision, lethargy, insomnia, memory disorder, sour taste, numbness
Respiratory	- difficulty breathing, pleural rub, worsening of pulmonary fibrosis
Urogenital	- haematuria

Postmarketing Surveillance

The following adverse events have been reported during post marketing surveillance.

- **Body as a Whole**
abdomen enlarged, asthenia, chills, fever, general pain, headache, infection, inflammation, photosensitivity reactions, swelling (temporal bone), jaundice
- **Cardiovascular System**
angina, bradycardia, cardiac arrhythmia, congestive heart failure, ECG changes/ischaemia, hypertension, hypotension, murmur, myocardial infarction, phlebitis, pulmonary emboli, stroke, sudden cardiac death, syncope/blackouts, tachycardia, thrombosis, transient ischaemic attack, varicose veins
- **Digestive System**
constipation, diarrhoea, dry mouth, duodenal ulcer, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, increased appetite, liver function tests abnormal, nausea, peptic ulcer, rectal polyps, thirst, vomiting
- **Endocrine**
diabetes, thyroid enlargement
- **Haemic and Lymphatic System**
anaemia, decreased WBC, ecchymosis, lymphedema, PT increased, PTT increased, platelets decreased, WBC decreased, WBC increased

- **Metabolic and Nutritional System**
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 System**
ankylosing spondylosis, joint disorders, joint pain, myalgia, pelvic fibrosis, spinal fracture, paralysis, tenosynovitis-like symptoms
- **Nervous System**
anxiety, convulsion, delusions, depression, dizziness, hypoesthesia, insomnia, lethargy, libido increased, lightheadedness, memory disorder, mood swings, nervousness, neuromuscular disorders, numbness, paresthesia, peripheral neuropathy, sleep disorders
- **Respiratory System**
cough, dyspnea, epistaxis, hemoptysis, 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, pruritis, rash, skin lesions, urticaria
- **Special Senses**
abnormal vision, amblyopia, blurred vision, dry eyes, hearing disorders, ophthalmologic disorders, taste disorders, tinnitus
- **Urogenital System**
bladder spasms, breast pain, breast tenderness, gynecomastia, hematuria, incontinence, 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, infection, inflammation, sterile abscess, induration and hematoma have been reported.

There have been very rare reports of suicidal ideation and attempt.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.

Dosage and Administration

Prostate Cancer

The recommended dose is 1 mg (0.2mL) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically.

Assisted Reproductive Techniques

Long protocol: the maximum recommended daily dose of leuprorelin acetate is 1mg (0.2mL) administered by subcutaneous injection. The treatment must be started in the luteal phase (approximately day number 20 of the previous cycle for which ovulation induction is wanted) and must be continued until the start of stimulation with human chorionic gonadotrophin (hCG) hormone. The duration of treatment is between 24 and 28 days, depending on the ovary response to exogenous gonadotrophin stimulus.

Short protocol: the recommended daily dose of leuprorelin acetate is 1 mg (0.2 mL) administered by subcutaneous injection. The treatment must be started at the beginning of the follicular phase (approximately day 1 of the cycle) and must continue until the administration of hCG hormone. The duration of treatment is between 12 and 14 days, depending on the ovarian response to exogenous gonadotrophin stimulus. In both protocols, when stimulation with exogenous gonadotrophins is started, the dose of leuprorelin acetate can be reduced to a daily dose of 0.5 mg (0.1 mL) administered by subcutaneous injection. The time of the day for the injection has to be constant during the entire treatment. As with all products administered subcutaneously the site of injection must be changed periodically.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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 dyspnoea, 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 (leuprorelin acetate injection) is a sterile solution supplied in multi-dose vials as follows: 2.8 mL (14 dose).

The vials will include a slight overage to facilitate the removal of product. Each 0.2 mL contains 1mg of leuprorelin acetate, sodium chloride for tonicity adjustment, 1.8mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Store at 2° C to 8° C (in a refrigerator) and store the vial in the outer carton. Do not freeze.

Further Information

Nil

Name and Address of the Sponsor

Abbott Laboratories (NZ) Ltd
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Auckland

Medicine Schedule

Prescription Only Medicine

Date of Preparation

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Version 01