PRODUCT INFORMATION

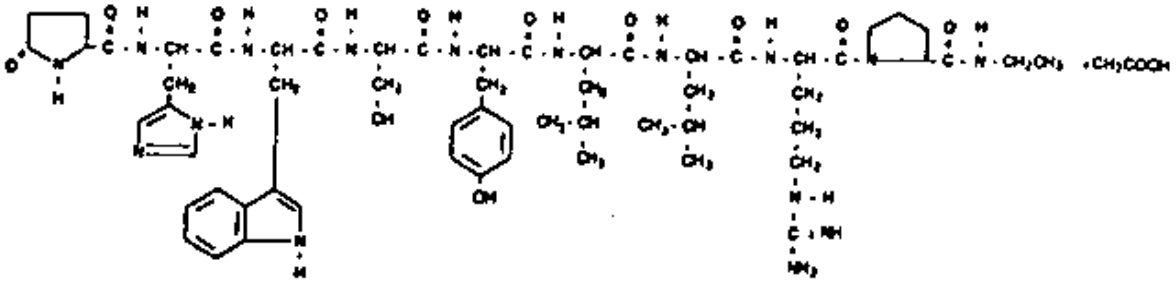
LUCRIN (LEUPRORELIN ACETATE) 5MG/ML

NAME OF THE MEDICINE

Non-proprietary Name

Leuprorelin acetate

Chemical Structure



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 5-0xo-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 oestradial 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. Leuprorelin has a plasma half-life of approximately 3 hours. The metabolism, distribution and excretion of leuprorelin in man have not been determined.

INDICATIONS

Lucrin (leuprorelin acetate) is indicated in the palliative treatment of metastatic or locally extensive prostatic cancer (Stage C and D).

CONTRAINDICATIONS

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

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

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

Leuprolide acetate injection is contraindicated in patients with known hypersensitivity to leuprolide acetate or similar nonapepetides 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 leuprorelin therapy under close supervision.

(See ADVERSE EFFECTS section)

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and-or glycosylated haemoglobin (HbA1c) periodically in patients receiving GnRH agonists and manage with current practice for treatment of hyperglycaemia or diabetes.

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

Effect on QT/QTc Interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating leuprorelin acetate.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of leuprorelin acetate with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide,procainamide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

Bone mineral density changes can occur during any hypoestrogenic state. Bone mineral density loss may be reversible after withdrawal of leuprorelin acetate.

Convulsions

Postmarketing reports of convulsions have been observed in patients on leuprorelin 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.

'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. Embryolethal 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.

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-orchiectomised 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.

INTERACTIONS WITH OTHER MEDICINES

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.

See PRECAUTIONS, *Effect on QT/QTc Interval* section.

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-orchiectomised 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, leuprorelin 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 leuprorelin 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 leuprorelin discontinued treatment for this reason. The administration of leuprorelin 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 flushes	51	11
Impotence	2	11
Gastrointestinal		
Anorexia	2	3
Constipation	3	1
Nausea/vomiting	5	16
Musculoskeletal		
Bone Pain	3	1
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 arrythmias, 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, tachycaridia, 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, serious liver injury

- ***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, delusions, depression, dizziness, hypoesthesia, insomnia, lethargy, libido increased, lightheadedness, memory disorder, mood swings, nervousness, neuromuscular disorders, numbness, paresthesia, peripheral neuropathy, sleep disorders, convulsion

- ***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

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.

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

OVERDOSAGE

In rats, subcutaneous administration of 250 to 500 times the recommended human dose results in dyspnoea, decreased activity, and local irritation at the injection site. There is no clinical

experience with the effects of an acute overdose of leuprorelin. Because the acute animal toxicity of the drug is low, adverse effects are not expected.

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26 and in New Zealand 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Lucrin (leuprorelin acetate injection) is a clear, sterile solution supplied in clear glass multi-dose vials. Each 5 mL vial contains 2.8 mL of solution (14 doses). The vial is packed inside an outer carton. Each carton contains one multi-dose vial.

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.

NAME AND ADDRESS OF THE SPONSOR

AbbVie Pty Ltd
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Mascot NSW 2020
Australia

POISON SCHEDULE OF THE MEDICINE

S4-Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 October 1991

DATE OF MOST RECENT AMENDMENT

24 February 2017

Version 15