NEW ZEALAND DATA SHEET

1. LUCRIN® 5 mg/mL SOLUTION FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 5 mg of leuprorelin acetate.

Excipients with known effect

Benzyl alcohol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

Lucrin is a sterile, clear aqueous solution intended for subcutaneous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prostate Cancer

Lucrin (leuprorelin 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 localised 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* fertilisation or other assisted reproductive technique options.

4.2 Dose and Method of Administration

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

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

Prostate Cancer

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

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.

Assisted Reproductive Techniques

Long protocol:
The maximum recommended daily dose of leuprorelin acetate is 1 mg (0.2 mL) 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 ovaric 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.

Paediatric Population

The safety and effectiveness of leuprorelin acetate daily injection in children has not been established.

4.3 Contraindications

Leuprorelin acetate injection is contraindicated in patients with known hypersensitivity to leuprorelin acetate or similar nonapeptides or any of the excipients listed in section 6.1.

Leuprorelin acetate is contraindicated in pregnancy due to its embryotoxic effects (see section 4.6 - Pregnancy).

Leuprorelin acetate should not be administered to a nursing mother as it is not known whether leuprorelin acetate is excreted into human milk (see section 4.6 - Lactation).

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

4.4 Special Warnings and Precautions

General

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 section 5.1).

Isolated cases of worsening of pre-existing signs and symptoms during the first weeks of treatment have been reported. Worsening of symptoms may contribute to paralysis with or without fatal complications. Patients with metastatic vertebral lesions and/or urinary tract obstruction should be closely observed during the first few weeks of treatment.

Bone Mineral Density

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

Convulsions

Post-marketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprorelin acetate. These included patients in the female and paediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumours, and in patients on concomitant medications that have been associated with convulsions such as bupropion and selective serotonin reuptake inhibitors (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 paraesthesia 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'.

Benzyl Alcohol

Patients with known allergies to benzyl alcohol, an ingredient of this medicine (see section 6.1), may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Men

Prostate Cancer

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving gonadotropin releasing hormone (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) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

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.

Women

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 acetategonadotrophins administered at the same dose can vary from woman to woman and between cycles in the same woman

4.5 Interactions with Other Medicines and Other Forms of 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 medicine is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Prostate Cancer

See section 4.4 – Men, Effect on QT/QTc Interval.

4.6 Fertility, Pregnancy and Lactation

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 to 10 micrograms/kg in rats and at 0.1 micrograms/kg in rabbits.

Pregnancy (Category D)

Leuprorelin is contraindicated in pregnancy due to its embryotoxic effects (see section 4.3).

Lactation

Leuprorelin acetate should not be administered to a nursing mother as it is not known whether leuprorelin acetate is excreted into human milk (see section 4.3).

4.7 Effects on Ability to Drive and Use Machines

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 Injection are known.

4.8 Undesirable 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 paraesthesia 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 diethylstilbestrol (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 treatment.

System Organ Class Adverse Reaction	**Lucrin** **(n=98)**	**DES** **(n=101)**
	Number of Reports	
Cardiovascular System		
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
Paraesthesia	3	0
Endocrine System		
Gynaecomastia/breast tenderness	3	49
Hot flushes	51	11
Impotence	2	11
Gastrointestinal System		
Anorexia	2	3
Constipation	3	1
Nausea/vomiting	5	16
Musculoskeletal System		
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:

System Organ Class	**Adverse Reaction**
Cardiovascular System	cardiac arrhythmias, myocardial infarction
Endocrine System	decreased testicular size
Gastrointestinal System	gastrointestinal bleeding
Haemic/Lymphatic System	decreased haematocrit and haemoglobin
Integumentary System	erythema and ecchymosis at the injection site, rash, hair loss, itching
Miscellaneous	aesthenia, increased BUN and creatinine, fatigue, fever, facial swelling
Musculoskeletal System	myalgia

Nervous System	blurred vision, lethargy, insomnia, memory disorder, sour taste, numbness
Respiratory System	difficulty breathing, pleural rub, worsening of pulmonary fibrosis
Urogenital System	haematuria

Post-Marketing Experience

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 and serious liver injury.
- **Endocrine:** diabetes, thyroid enlargement.
- **Haemic and Lymphatic System:** anaemia, decreased WBC, ecchymosis, lymphoedema, PT increased, PTT increased, platelets decreased, WBC decreased, WBC increased.
- **Metabolic and Nutritional System:** BUN increased, calcium increased, creatinine increased, dehydration, oedema, hyperlipidaemia (total cholesterol, LDL-cholesterol, triglycerides), hyperphosphataemia, hypoglycaemia, hypoproteinaemia, 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, paraesthesia, peripheral neuropathy, sleep disorders.
- **Respiratory System:** 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, urticarial.
- **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, haematuria, 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 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.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is no clinical experience with the effects of an acute overdose of leuprorelin acetate injection. 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 overdose, the patients should be monitored closely and management should be symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Information Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Gonadotrophin-Releasing Hormone Analogues, ATC Code: L02AE 02.
Lucrin (leuprorelin acetate) 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 acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given on a continuous basis and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprorelin acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate has resulted in inhibition of the growth of certain hormone dependent tumours (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 down-regulation of the gonadotropin receptors, is suggested in some animal studies.

In humans, subcutaneous administration of single daily doses of leuprorelin acetate 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 acetate results in decreased levels of LH and FSH and sex hormones in all patients. In males, testosterone is reduced to castrate or pre-pubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating drug therapy at recommended doses.

Prostate Cancer

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.

Assisted Reproduction

As with other GnRH analogues, isolated cases of ovary hyperstimulation have been reported associated with the use of leuprorelin 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 leuprorelin 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.

5.2 Pharmacokinetic Properties

Leuprorelin is not active when administered orally.

Absorption

In one study, bioavailability by subcutaneous administration was found to be comparable to intravenous administration.

Distribution

The mean steady-state volume of distribution of leuprorelin acetate 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 acetate administered intravenously, revealed that the mean systemic clearance was 7.6 L/hour, with a terminal elimination half-life of approximately three hours based on a two compartment model.

Animal studies have shown ^{14}C-labeled leuprorelin acetate was metabolised into smaller inactive peptides, a pentapeptide (Metabolite I) tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further metabolised.

The major metabolite (M-I) plasma concentrations measured in five prostate cancer patients given leuprorelin acetate depot suspension reached a maximum concentration two to six hours after dosing and

were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprorelin concentrations.

Excretion

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

Special Populations

The pharmacokinetics of leuprorelin acetate in hepatic and renal impaired patients has not been determined.

5.3 Preclinical Safety Data

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 4 mg/kg/day). This study also revealed a significant but not a dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males in (highest incidence in the low dose group). In mice, no leuprorelin acetate-induced tumours 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.

In short term toxicity studies in mice treated for 3 months with 20 to 200 mg/kg/day, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride
Benzyl alcohol
Glacial acetic acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years.

6.4 Special Precautions for Storage

Store at 2° C to 8°C (Refrigerate, do not freeze). Store vial in the outer carton to protect from light.

6.5 Nature and Contents of Container

Lucrin (leuprorelin acetate) injection is a sterile solution supplied in a multi-dose 2.8 mL glass vial with rubber stopper containing 14 mg of leuprorelin acetate.

6.6 Special Precautions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand
Phone No.: 0800 900 030.

9. DATE OF FIRST APPROVAL

5 December 1985

10. DATE OF REVISION OF THE TEXT

08 February 2018

Version 05

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
All sections	Adoption of the new Medsafe Data Sheet SPC-style format and content requirements according to NZDS Explanatory Guide, effective from 1 March 2017.
Section 4.2 Dosage and Administration and Section 5.1 Pharmacodynamics	These sections were updated with Castration-Resistant Prostate Cancer (CRPC) verbiage. The text now aligns with the current standard of care for the CRPC prostate cancer patients who are to continue gonadal suppression with GnRH agonists when on additional therapies.
Section 4.4 Special Warnings and Precautions	A general precautionary statement concerning a rise in hormone levels in early phase treatment leuprorelin acetate is added in line with the LUCRIN Company Core Data Sheet and the approved LUCRIN Depot Data Sheet, .
Section 4.4. Special Warnings and Precaution, Convulsions sub-section	This section was edited to generalize the statement directing it to the drug class, GnRH agonists, in addition of the leuprorelin acetate.
Section 4.4 Special Warnings and Precautions, Benzyl alcohol sub-section	This section was edited to include a precaution concerning the excipient ingredient, benzyl alcohol, contained in the Lucrin Injection formulation in line with LUCRIN Company Core Data Sheet.
Section 5.2 Pharmacokinetic Properties	This section has been expanded to include information on metabolism, distribution, and excretion in line with the LUCRIN Company Core Data Sheet and approved LUCRIN Depot Data Sheet.