SCHEDULING STATUS

S4

1 NAME OF MEDICINE

LUCRIN DEPOT 3,75 mg PDS Lyophilised microspheres and sterile diluent suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LUCRIN DEPOT 3,75 mg PDS: Each single-dose prefilled dual-chambered syringe contains leuprolide acetate 3,75 mg and 1 mL of sterile diluent for injection

Contains mannitol (sugar-alcohol)

For full lists of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Front chamber: White powder.

After reconstitution: White suspension which on standing deposits a white sediment which is readily re-suspended on shaking.

Rear chamber: Colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LUCRIN DEPOT 3,75 mg PDS is indicated in:

Endometriosis

The management of endometriosis, including pain relief and reduction of endometriotic lesions, in women of 18 years of age and older, for a period of 6 months.

Prostate Cancer

The palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or oestrogen administration is either not indicated or unacceptable to the patient.

Breast Cancer

Adjuvant therapy to surgery in breast carcinoma.

Central Precocious Puberty

Treatment of children with central precocious puberty (CPP).

4.2 Posology and method of administration

LUCRIN DEPOT 3,75 mg PDS must be administered under the supervision of a medical practitioner.

Endometriosis

The recommended dose of LUCRIN DEPOT 3,75 mg PDS in the treatment of endometriosis is 3,75 mg.

Prostate Cancer

The recommended dose of LUCRIN DEPOT 3,75 mg PDS in the palliative treatment of advanced prostatic carcinoma is 3,75 mg administered subcutaneously once a month.

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.

Breast Cancer

The recommended dose of LUCRIN DEPOT 3,75 mg PDS as adjuvant therapy to surgery in breast cancer is 3,75 mg administered 4-weekly as a single intramuscular or subcutaneous injection.

Central Precocious Puberty

The recommended dose for the treatment of children with central precocious puberty must be individualised for each child based on a mg/kg ratio of medicine to body weight. Younger children require higher doses on a mg/kg ratio.

For each dosage form, after one to two months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, determination of 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 are 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 3,75 mg PDS should be considered before age 11 for females and age 12 for males.

Administration Guidelines for Central Precocious Puberty

Initial Dose

The recommended starting dose of LUCRIN DEPOT 3,75 mg PDS is 0,3 mg/kg for four weeks (minimum 7,5 mg), administered intramuscularly or subcutaneously.

The following physiologic effects have been noted with the chronic administration of leuprolide 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.

The starting dose will be dictated by the child's weight as follows:

Child's Weight	Actual Dosage	Number of Injections	Total Dosage
≤ 25,0 kg	3,75 mg x 2	1	7,5 mg
25,0 – 37,5 kg	3,75 mg x 3	2	11,25 mg
> 37,5 kg	3,75 mg x 4	2	15,0 mg

Note: When multiple injections are required to achieve the desired total dosage, they should be administered at the same time.

Maintenance Dose

If total downregulation is not achieved, the dose should be titrated upward in increments of 3, 75 mg every four weeks. This dose will be considered the maintenance dose.

4.3 Contraindications

LUCRIN DEPOT 3,75 mg PDS is contraindicated in:

- Patients with known hypersensitivity to leuprolide acetate or similar nonapeptides or to any of the excipients in LUCRIN DEPOT 3,75 mg PDS.
- Patients with undiagnosed, abnormal vaginal bleeding.
- Women who are or may become pregnant while receiving LUCRIN DEPOT 3,75 mg PDS (see section 4.6).
- Women who are breastfeeding (see section 4.6).
- Children demonstrating hypersensitivity to GnRH, LUCRIN DEPOT 3,75 mg PDS or excipients.

Cases of anaphylaxis have been reported with the monthly formulation of LUCRIN DEPOT 3,75 mg PDS.

4.4 Special warnings and precautions for use

All Populations

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of LUCRIN DEPOT 3,75 mg PDS. Therefore, an increase in clinical signs and symptoms may be observed. Worsening of pre-existing signs and symptoms during the first weeks of treatment may occur. Worsening of symptoms may contribute to paralysis with or without fatal complications.

Bone Mineral Density

Decreased bone mineral density can occur in women and in men. There is no data in men regarding reversibility after withdrawal of LUCRIN DEPOT 3,75 mg PDS.

In women, bone mineral density loss may or may not be reversible after withdrawal of LUCRIN DEPOT 3,75 mg PDS (see section 4.8).

Convulsions

Postmarketing reports of convulsions have been observed in patients on LUCRIN DEPOT 3,75 mg PDS therapy. 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 medicines 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.

Women

Endometriosis

LUCRIN DEPOT 3,75 mg PDS should not be administered to patients with undiagnosed abnormal vaginal bleeding.

Pregnancy must be excluded before starting with treatment. LUCRIN DEPOT 3,75 mg PDS is contraindicated in pregnancy. When used monthly at the recommended dose, LUCRIN DEPOT 3,75 mg PDS usually inhibits ovulation and stops menstruation.

However, taking LUCRIN DEPOT 3,75 mg PDS does not ensure contraception. Therefore, patients should use non-hormonal methods of contraception. Patients should be advised to see their doctor if they believe they may be pregnant.

If a patient becomes pregnant during treatment, LUCRIN DEPOT 3,75 mg PDS must be discontinued and the patient must be apprised of the potential risk of the foetus.

During the early phase of therapy in endometriosis, sex steroids temporarily rise above baseline because of the physiologic effect of LUCRIN DEPOT 3,75 mg PDS. Therefore, an increase in the clinical signs and symptoms may be observed during the initial days of therapy, but these dissipate with continued therapy at adequate doses.

Men

Prostate Cancer

Flare effect

Worsening of signs and symptoms during the first weeks of treatment of prostate cancer may occur with LUCRIN DEPOT 3,75 mg PDS. Patients may experience a temporary increase in bone pain, which should be managed symptomatically. Cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. For patients at risk, the medical practitioner may consider initiating therapy with daily (short-acting) LUCRIN injections for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists such as LUCRIN DEPOT 3,75. 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 LUCRIN DEPOT 3,75, 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 such as LUCRIN DEPOT 3,75 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 LUCRIN DEPOT 3,75 should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases who may develop paraesthesia or paralysis 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.

Effect on QT/QTc Interval

LUCRIN DEPOT 3,75 mg PDS deprivation treatment may prolong the QT interval in patients with a history of, or risk factors for, QT prolongation. Torsade de pointes has been reported in association with LUCRIN DEPOT 3,75 mg PDS.

The concomitant use of LUCRIN DEPOT 3,75 mg PDS with medicines known to prolong the QT interval or able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines, methadone, macrolide antibiotics, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

Changes in Laboratory values during treatment

Response to leuprolide acetate, should be monitored by measuring serum levels of testosterone as well as prostate-specific antigen and prostatic 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. Transient increases in acid phosphatase levels have occurred early in treatment. However, by the fourth week, the elevated levels usually decrease to values at or near baseline.

During clinical trials isolated elevations of SGOT (ALT) were observed. In clinical trials LUCRIN DEPOT 3,75 mg PDS was associated with elevation of total cholesterol, triglycerides, lactate

dehydrogenase (LDH) and phosphorous and decreases in high-density lipoprotein (HDL) and white blood cell (WBC) counts.

Children

Central Precocious Puberty

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with rapidly advancing ventral precocious puberty.

Laboratory tests

Response to LUCRIN DEPOT 3,75 mg PDS 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.

Information for parents

Prior to starting therapy with LUCRIN DEPOT 3,75 mg PDS, the parent(s) or guardian(s) must be made aware of the importance of continuous therapy. Adherence to four-week medicine administration schedules must be complied with if therapy is to be successful.

Noncompliance with LUCRIN DEPOT 3,75 mg PDS 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.

- During the first two months of therapy, a female may experience menses or spotting. If bleeding continues beyond the second month, notify the medical practitioner.

- Any irritation at the injection site should be reported to the medical practitioner immediately.

- Any unusual signs or symptoms should be reported to the medical practitioner.

Bone Mineral Density

Bone mineral density (BMD) may decrease during GnRH therapy in children with central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Pseudotumor cerebri/idiopathic intracranial hypertension

Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension has been reported in paediatric patients receiving leuprorelin acetate, but it cannot be ruled out that it may also occur in adults. Monitor patients for signs and symptoms of PTC, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. Refer the patient to an ophthalmologist to confirm the presence of papilledema. If PTC is confirmed, treat the patient in accordance to the established treatment guidelines and permanently discontinue use of leuprorelin acetate.

Impairment of fertility

Studies in adults with LUCRIN DEPOT 3,75 mg PDS have shown reversibility of fertility suppression when the medicine was discontinued after continuous administration for period of up to 24-weeks.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic-based interaction studies have not been conducted with LUCRIN DEPOT 3,75 mg PDS. However, due to LUCRIN DEPOT 3,75 mg PDS being a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies,

and due to this compound being only 46 % bound to plasma proteins, medicine interactions are not expected to occur.

Prostate Cancer

See section 4.4.

Medicine/Laboratory Test Interactions

Diagnostic tests of pituitary gonadotropic and gonadal function conducted during treatment and up to 4 to 8 weeks after discontinuation of LUCRIN DEPOT 3,75 mg PDS therapy may be misleading, as therapeutic doses of LUCRIN DEPOT 3,75 mg PDS result in suppression of the pituitary-gonadal system.

4.6 Fertility, pregnancy and lactation

Pregnancy

LUCRIN DEPOT 3,75 mg PDS is contraindicated during pregnancy or lactation (see section 4.3). The safety of leuprolide acetate in pregnancy has not been established.

Breastfeeding

Mothers on LUCRIN DEPOT 3,75 mg PDS should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

LUCRIN DEPOT 3,75 mg PDS may cause convulsions, blurred vision or dizziness that may impair the patient’s ability to drive or to use machinery.

4.8 Undesirable effects

Women:

The most common adverse events in women are associated with the pharmacological actions of LUCRIN on the steroidogenesis:

SYSTEM ORGAN CLASS	**ADVERSE EVENTS**
Metabolism and nutrition disorders	Weight gain, weight loss
Psychiatric disorders	Loss or decreased libido, increased libido, affect lability
Nervous system disorders	Headache
Vascular disorders	Hot flushes, vasodilatation, hypotension
Skin and subcutaneous tissue disorders	Acne, seborrhoea, dry skin, urticaria, skin odour abnormal, hyperhydrosis, hair growth abnormal, hirsutism, hair disorder, eczema, nail disorder, night sweats
Reproductive system and breast disorders	Vaginal haemorrhage, dysmenorrhoea, menstrual disorder, breast enlargement, breast engorgement, breast atrophy, genital discharge, vaginal discharge, galactorrhoea, breast pain, metrorrhagia, menopausal symptoms, dyspareunia, uterine disorder, vulvovaginitis, menorrhagia
General disorders and administration site conditions	Feeling hot, irritability

Investigations	Bone density decreased
Long exposure (6 to 12 months)	Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis

Changes in Bone Density

In controlled clinical studies, patents with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with **LUCRIN DEPOT 3,75 mg PDS**. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3,9 % at six months compared with the pretreatment value. For those patients who were tested at six or twelve months after discontinuation of therapy, mean bone density returned to within 2 % of pre-treatment. When **LUCRIN DEPOT 3,75 mg PDS** was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2,7 % compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed.

Table 1 presents ADRs and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); unknown (unable to estimate frequency based upon available data) from endometriosis and breast cancer clinical studies.

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 agonist and these events.

TABLE 1: ADVERSE EVENTS REPORTED IN ENDOMETRIOSIS AND BREAST CANCER CLINICAL STUDIES

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
Infections and infestations	Infection	Uncommon	
	Upper respiratory tract infection		Uncommon
	Pyelonephritis	Uncommon	
	Furuncle	Uncommon	
	Urinary tract infection		Common
	Nasopharyngitis		Common
Blood and lymphatic system disorder	Leukopenia		Uncommon
	Iron deficiency anaemia		Common
Metabolism and nutrition disorders	Anorexia	Uncommon	Uncommon
	Increased appetite	Uncommon	Very common
	Decreased appetite		Common
	Hypercholesterolaemia	Common	
	Abnormal weight gain	Very common	Very common
	Abnormal loss of weight	Common	Very common
Psychiatric disorders	Affect lability	Very common	Common
	Mood swings		Very common
	Personality disorders	Uncommon	

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Nervousness	Very common	Very common
	Libido decreased	Very common	
	Insomnia	Very common	Very common
	Sleep disorder		Common
	Depression	Very common	Very common
	Major depression	Common	
	Anxiety	Common	Common
	Delusions	Uncommon	
	Abnormal thinking	Uncommon	
	Confusional state	Common	
	Euphoric mood	Uncommon	
	Hostility	Common	
	Apathy	Uncommon	
	Nervousness/anxiety	Very common	
Nervous system disorders	Dizziness	Very common	Very common
	Dizziness postural		Common
	Headache	Very common	Very common
	Paraesthesia	Common	Common
	Somnolence	Uncommon	Common
	Amnesia	Uncommon	

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Syncope	Uncommon	
	Migraine	Common	
	Hypertonia	Common	
	Ataxia	Uncommon	
	Tremor		Common
	Convulsions local		Common
Eye disorders	Vision blurred		Common
	Eye disorder	Uncommon	
	Visual impairment	Common	
	Amblyopia	Common	
	Eye pain	Uncommon	
	Conjunctivitis		Common
Ear and labyrinth disorders	Vertigo	Common	
	Tinnitus		Common
Cardiac disorders	Tachycardia	Uncommon	
	Palpitations	Common	Common
Vascular disorders	Hot flush		Very common
	Vasodilatation	Very common	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon	Common

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Dyspnoea		Common
	Dysphonia	Uncommon	
	Cough		Common
	Oropharyngeal pain		Common
Gastrointestinal disorders	Constipation	Common	Common
	Nausea	Very common	Very common
	Vomiting		Common
	Nausea and vomiting	Common	
	Abdominal distention	Uncommon	
	Diarrhoea	Common	Common
	Dyspepsia	Uncommon	
	Flatulence	Uncommon	
	Gastritis	Uncommon	
	Gingival bleeding	Uncommon	
	Dry mouth	Common	
	Abdominal pain	Common	Common
	Abdominal pain upper		Common
	Abdominal pain lower		Common
	Stomatitis		Common
	Retching		Common

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Abdominal discomfort		Common
	Tongue disorder		Common
Hepatobiliary disorder	Liver tenderness	Uncommon	
Skin and subcutaneous tissue disorders	Erythema		Common
	Alopecia	Common	Common
	Ecchymosis	Common	
	Acne	Very common	Common
	Seborrhoea	Common	
	Rash	Common	
	Rash maculo-papular	Uncommon	
	Dry skin	Common	
	Photosensitivity reactions	Uncommon	
	Urticaria		Common
	Hyperhidrosis	Common	Very common
	Hirsutism	Common	
	Hair disorders	Uncommon	
	Night sweats		Common
	Pigmentation disorder		Common
Musculoskeletal and connective tissue disorders	Bone pain		Common
	Myalgia	Uncommon	

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Arthropathy	Common	
	Arthralgia	Common	Very common
	Back pain	Common	Very common
	Arthritis	Uncommon	
	Nuchal rigidity	Common	
	Neck pain	Common	Common
	Muscular weakness		Common
	Musculoskeletal stiffness		Common
	Periarthritis		Common
Renal and urinary disorders	Urinary incontinence	Uncommon	
	Dysuria	Common	
	Pollakiuria	Uncommon	Common
	Nocturia		Common
Reproductive system and breast disorders	Dysmenorrhoea		Common
	Breast enlargement	Uncommon	
	Breast engorgement	Uncommon	
	Breast atrophy	Common	
	Genital discharge	Common	
	Galactorrhoea	Uncommon	
	Breast pain	Common	

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Pelvic pain	Common	
	Metrorrhagia		Common
	Menopausal symptoms		Common
	Vulvovaginitis	Very common	Common
	Menorrhagia		Common
General disorders and administration site conditions	Pain	Common	
	Chest pain	Common	Common
	Oedema	Common	Common
	Oedema peripheral	Common	Common
	Face oedema	Uncommon	
	Generalised oedema	Uncommon	
	Asthenia	Common	Very common
	Fatigue		Common
	Pyrexia		Common
	Injection site reaction	Uncommon	Common
	Injection site mass	Uncommon	
	Injection site pain	Common	Very common
	Injection site induration		Very common
	Injection site pruritus		Common
	Injection site erythema		Common

System Organ Class	Preferred Term	Endometriosis 3,75 mg	Breast Cancer 3,75 mg
		Frequency	
	Injection site haemorrhage		Common
	Chills	Common	
	Injection site hypersensitivity	Uncommon	
	Thirst	Common	
	General physical health deterioration		Very common
	Feeling hot		Very common
	Irritability		Common
	Malaise		Common
Investigations	Body temperature increased		Uncommon

Prostate Cancer

The most common adverse events in men are associated with the pharmacological actions of LUCRIN on the steroidogenesis:

SYSTEM ORGAN CLASS	ADVERSE EVENTS
Neoplasm benign, malignant and unspecified (including cysts and polyps)	Prostate tumour flare, aggravation of prostate cancer
Metabolism and nutrition disorders	Weight gain, weight loss
Psychiatric disorders	Loss or decreased libido, increased libido

Nervous system disorders	Headache, muscular weakness
Vascular disorders	Vasodilatation, hot flushes, hypotension, orthostatic hypotension
Skin and subcutaneous tissue disorders	Dry skin, hyperhydrosis, rash, urticaria, hair growth abnormal, hair disorder, night sweats, hypotrichosis, pigmentation disorders, cold sweats, hirsutism
Reproductive system and breast disorders	Gynaecomastia, breast tenderness, erectile dysfunction, testicular pain, breast enlargement, breast pain, prostate pain, penile swelling, penis disorders, testis atrophy
General disorders and administration site conditions	Mucosal dryness
Investigations	PSA increased, bone density decreased
Long exposure (6 to 12 months)	Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis

Men

In the majority of patients testosterone levels increase above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms (see section 4.4).

Table 2 presents all adverse drug reactions (ADR) and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100) not known (unable to estimate frequency based upon available data) from prostate cancer clinical studies.

TABLE 2: ADVERSE EVENTS REPORTED IN PROSTATE CANCER CLINICAL STUDIES

System Organ Class	Frequency	Adverse events
Infections and infestations	Uncommon	Rhinitis, fungal skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Neoplasm
Metabolism and nutrition disorders	Common	Anorexia
	Uncommon	Hyperglycaemia, abnormal weight gain
Psychiatric disorders	Common	Libido decreased
	Uncommon	Insomnia, sleep disorders, depression
Nervous system disorders	Uncommon	Dizziness, paraesthesia, somnolence
Eye disorders	Uncommon	Amblyopia
Ear and labyrinth disorders	Uncommon	Ear pain, tinnitus

System Organ Class	Frequency	Adverse events
Cardiac disorders	Uncommon	Dysrhythmia, angina pectoris, ventricular extrasystoles
Vascular disorders	Very Common Uncommon	Hot flushes, vasodilatation Angiopathy, hypertension, poor peripheral circulation
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Epistaxis, haemoptysis, emphysema
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis, pruritus
	Uncommon	Alopecia, rash, rash maculo-papular, hair disorders, night sweats
Musculoskeletal and connective tissue disorders	Common	Arthralgia
	Uncommon	Bone pain, myalgia, muscular weakness, pain in extremity
Renal and urinary disorders	Uncommon	Dysuria, pollakiuria, haematuria, urinary retention, polyuria
Reproductive system and breast disorders	Common	Erectile dysfunction, testicular atrophy
	Uncommon	Gynaecomastia, breast enlargement
General disorders and administration site conditions	Common	Pain, injection site pain, oedema peripheral, fatigue, injection site induration

System Organ Class	Frequency	Adverse events
	Uncommon	Chest pain, asthenia, injection site inflammation, injection site erythema, injection site irritation, chills
Investigations	Very Common	Blood lactic dehydrogenase increased
	Common	Aspartate aminotransferase increased/AST, blood alkaline phosphatase increased
	Uncommon	Haemoglobin decreased, blood urea increased, blood uric acid increased, blood calcium increased, alanine aminotransferase increased / ALT, gamma-glutamyltransferase increased, platelet count decreased, protein urine present, white blood cell count increased, reticulocyte count increased

Central Precocious Puberty

The most common adverse events are associated with the pharmacological actions of LUCRIN on the steroidogenesis:

SYSTEM ORGAN CLASS	ADVERSE EVENTS
Psychiatric disorders	Affect lability
Nervous system disorders	Headache
Vascular disorders	Vasodilatation

Skin and subcutaneous tissue disorders	Acne/seborrhoea, rash including erythema multiforme
Reproductive system and breast disorders	Vaginal haemorrhage, vaginal discharge, vulvovaginitis
General disorders and administration site conditions	Pain, injection site reactions including abscess

Table 3 presents ADRs and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); unknown (unable to estimate frequency based upon available data) from CPP clinical studies.

TABLE 3: ADVERSE EVENTS REPORTED IN CENTRAL PRECOCIOUS PUBERTY CLINICAL STUDIES

System Organ Class	**Frequency**	**Adverse events**
Infections and infestation	Uncommon	Infection, rhinitis, influenza, pharyngitis, sinusitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Cervix neoplasm
Immune system disorders	Uncommon	Hypersensitivity
Endocrine disorders	Uncommon	Precocious puberty, goiter
Metabolism and nutrition disorders	Common	Growth retardation, abnormal weight gain
	Uncommon	Increased appetite
Psychiatric disorders	Common	Affect lability

System Organ Class	Frequency	Adverse events
	Uncommon	Nervousness, depression
Nervous system disorders	Common	Headache
	Uncommon	Somnolence, syncope, hyperkinesia
Cardiac disorders	Uncommon	Bradycardia
Vascular disorders	Common	Vasodilatation
	Uncommon	Hypertension, peripheral vascular disorder
Respiratory, thoracic and mediastinal disorders	Uncommon	Epistaxis, asthma
Gastrointestinal disorders	Uncommon	Constipation, nausea and vomiting, dysphagia, gingivitis, dyspepsia
Skin and subcutaneous tissue disorders	Common	Rash, acne, skin odour abnormal
	Uncommon	Alopecia, hirsutism, hair disorder, nail disorder, leukoderma, skin hypertrophy, purpura
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia, arthropathy, myopathy, arthralgia
Renal and urinary disorders	Uncommon	Urinary incontinence
Reproductive system and breast disorders	Common	Gynaecomastia, vulvovaginitis
	Uncommon	Vaginal haemorrhage, cervix disorder, dysmenorrhoea, menstrual disorders, breast enlargement, vaginal discharge, breast pain, acquired feminisation

System Organ Class	Frequency	Adverse events
General disorders and administration site conditions	Common	Injection site reaction (with abscess), pain
	Uncommon	Peripheral oedema, pyrexia, hypertrophy, conditions aggravated
Investigations	Uncommon	Antinuclear antibody positive, red blood cell sedimentation rate increased

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty

System Organ Class	Adverse Event
Infections and infestations	Infection
	Urinary tract infection
	Pharyngitis
	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer
Blood and lymphatic system disorder	Anaemia [b, c]
Immune system disorders	Anaphylactic reaction
Endocrine disorders	Goiter

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Pituitary apoplexy
Metabolism and nutrition disorders	Diabetes mellitus
	Increased appetite
	Hypoglycaemia
	Dehydration
	Hyperlipidaemia
	Hyperphosphataemia
	Hypoproteinaemia
Psychiatric disorders	Mood swings[a]
	Nervousness
	Libido increased
	Insomnia
	Sleep disorder
	Depression[a]

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Anxiety
	Delusion
	Suicidal ideation [b, c]
	Suicide attempt [b, c]
Nervous system disorders	Dizziness
	Headache
	Paraesthesia
	Lethargy
	Memory impairment
	Dysgeusia
	Hypoaesthesia
	Syncope
	Neuropathy peripheral
	Cerebrovascular accident

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Loss of consciousness
	Transient ischemic attack [b, c]
	Paralysis
	Neuromyopathy
	Pseudotumor cerebri/idiopathic Intracranial hypertension[d]
	Convulsion
Eye disorders	Vision blurred
	Eye disorder
	Visual impairment
	Amblyopia
	Dry eye
Ear and labyrinth disorders	Tinnitus
	Hearing impaired

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
Cardiac disorders	Cardiac failure congestive [b, c]
	Dysrhythmia
	Myocardial infarction [b, c]
	Angina pectoris [b, c]
	Tachycardia
	Bradycardia
	Sudden cardiac death[b]
Vascular disorders	Hot flushes [d]
	Lymphoedema
	Hypertension
	Phlebitis [b, c]
	Thrombosis
	Flushing [d]
	Hypotension

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Varicose vein [b, c]
Respiratory, thoracic and mediastinal disorders	Pleural rub [b, c]
	Pulmonary fibrosis [b, c]
	Epistaxis
	Dyspnoea
	Haemoptysis [b, c]
	Cough
	Pleural effusion [b, c]
	Lung infiltration [b, c]
	Respiratory disorder
	Sinus congestion
	Pulmonary embolism [b, c]
	Interstitial lung disease [b, c]
Gastrointestinal disorders	Constipation

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Nausea
	Vomiting
	Gastrointestinal haemorrhage
	Abdominal distention
	Abdominal pain [d]
	Diarrhoea
	Dysphagia
	Dry mouth
	Duodenal ulcer [b, c]
	Gastrointestinal disorder
	Peptic ulcer
	Rectal polyp [b, c]
Hepatobiliary disorder [b, c]	Hepatic function abnormalities [b, c]
	Serious liver injury [b, c]

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Jaundice [b, c]
Skin and subcutaneous tissue disorders	Alopecia
	Ecchymosis
	Rash
	Dry skin
	Photosensitivity reaction
	Urticaria
	Dermatitis
	Hair growth abnormal
	Pruritus
	Pigmentation disorder
	Skin lesion
	Hyperhidrosis [d]
Musculoskeletal and connective tissue disorders	Myalgia

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Bone swelling
	Arthropathy
	Arthralgia
	Ankylosing spondylitis [b, c]
	Tenosynovitis
Renal and urinary disorders	Urinary incontinence
	Pollakiuria
	Micturition urgency
	Haematuria
	Bladder spasm [b, c]
	Urinary tract disorder [b, c]
	Urinary tract obstruction [b, c]
Reproductive system and breast disorders	Breast tenderness
	Gynaecomastia [b, d]

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Vaginal haemorrhage [c, d]
	Testicular atrophy [b, d]
	Testicular pain [b]
	Testicular disorder [b, d]
	Menstrual disorder [c, d]
	Breast pain
	Penile swelling [b]
	Penis disorder [b]
	Prostatic pain [b, d]
	Metrorrhagia [c, d]
General disorders and administration site conditions	Pain
	Chest pain [d]
	Oedema
	Asthenia

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Pyrexia
	Injection site reaction
	Injection site inflammation
	Injection site pain
	Injection site induration
	Injection site abscess sterile
	Injection site haematoma
	Chills
	Nodule
	Thirst
	Weight increased [d]
	Inflammation [c, b]
	Pelvic fibrosis [c, b]
Investigations	Blood urea increased

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	Blood uric acid increased
	Blood creatinine increased
	Blood calcium increased [b, c]
	Abnormal electrocardiogram [b, c]
	ECG signs of myocardial ischemia [b, c]
	Liver function test abnormal
	Decreased platelet count [b, c]
	Decreased blood potassium [b, c]
	White blood cell count increased
	Decreased white blood cell count [b, c]
	Prolonged prothrombin time [b, c]
	Prolonged activated partial thromboplastin time [b, c]
	Cardiac murmur
	Increased low density

Table 4. Post-marketing Experience Adverse Events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty	
System Organ Class	**Adverse Event**
	lipoprotein [b, c]
	Increased blood triglycerides [b, c]
	Increased blood bilirubin [b, c]
Injury, poisoning and procedural complications	Spinal fracture
[a] Depression and mood swing are commonly observed adverse reactions with long term use of GnRH agonists. [b] Only in men/prostate cancer population [c] Only in women/Endo and breast cancer populations [d] Only in children/CPP population	

Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists, including LUCRIN DEPOT 3,75 mg PDS. Post-marketing reports with this class of medicines include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression. A definitive cause and effect relationship between the treatment with GnRH agonists and the occurrence of these events has not been established. Monitoring for development or worsening of psychiatric symptoms during treatment with LUCRIN DEPOT 3,75 mg PDS is recommended.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

You can also report side effects to AbbVie (Pty) Ltd via this e-mail address: MEAPV@abbvie.com

4.9 Overdose

In overdose, side effects would be exacerbated and exaggerated (see section 4.4 and section 4.8). Treatment is symptomatic and supportive

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

A 21.10 – Tropic hormones

Leuprolide acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH).

Leuprolide acetate, a GnRH agonist, acts as an inhibitor of gonadotropin. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroideogenesis. This effect is reversible on discontinuation of therapy.

Administration of leuprolide 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 estrone and estradiol in pre-menopausal females).

However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH and sex steroids. In males, testosterone is reduced to castration or prepubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels.
During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of LUCRIN DEPOT 3,75 mg PDS.
These hormonal changes occur within a month of initiating medicine therapy at recommended doses.

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

Castration Resistant Prostate Cancer
In patients with metastatic castration-resistant prostate cancer, clinical studies have shown benefit from the addition of medicines 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.

5.2 Pharmacokinetic properties

Leuprolide acetate is not active when given orally. Bioavailability of leuprolide acetate following subcutaneous administration is comparable to that after intramuscular administration.

Absorption

Following a single administration of leuprolide acetate for depot suspension in prostatic carcinoma patients, doses of 3,75 mg and 7,5 mg by subcutaneous and intramuscular routes provided mean leuprolide acetate plasma concentrations at the end of one month of 0,7 ng/mL and 1,0 ng/mL, respectively. There was no indication of any medicine accumulation.

Serum levels of leuprolide acetate 3,75 mg were measured in 11 patients with pre-menopausal breast cancer over 12 weeks.

Mean leuprolide acetate levels were above 0, 1 ng/mL after four weeks and remained stable after re-injection (at 8 and 12 weeks). There was no tendency for medicine accumulation.

Distribution

The mean steady-state volume of distribution of leuprolide 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 leuprolide administered intravenously, revealed that the mean systemic clearance was 7,6 L/h, with a terminal elimination half-life of approximately three hours based on a two compartment model.

Animal studies have shown ^{14}C-labeled leuprolide 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 leuprolide acetate depot suspension reached a 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-I concentrations were approximately 20 % of mean leuprolide concentrations.

Excretion

Following administration of leuprolide 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 this product has not been determined in patients with hepatic or renal impairment.

Paediatric Patients

In a study of 22 children with central precocious puberty, doses of leuprolide acetate for Depot Suspension were given every four weeks and plasma levels were determined according to weight categories as summarised below.

Patient Weight Range (kg)	**Group Weight Average (kg)**	**Dose (mg)**	**Trough Plasma Leuprolide Level mean ± SD (ng/mL)***
20,2 – 27,0	22,7	7,5	0,77 ± 0,33
28,4 – 36,8	32,5	11,25	1,25 ± 1,06
39,3 – 57,5	44,2	15,0	1,59 ± 0,65

* Group average values determined at Week 4 immediately prior to leuprolide injection.

Medicine levels at 12 and 24 weeks were similar to respective 4-week levels

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LUCRIN DEPOT 3,75 mg PDS Lyophilised microspheres for suspension for injection:

Copoly (DL-Lactic acid/glycolic acid) (PLGA)

Mannitol

Gelatine

LUCRIN DEPOT 3,75 mg PDS Sterile diluent for suspension for injection**:**

Mannitol

Polysorbate 80

Sodium carboxymethylcellulose

Water for injection

Acetic acid, Glacial (pH adjuster)

6.2 Incompatibilities

No other fluid should be used for reconstitution of LUCRIN DEPOT 3,75 mg PDS mg.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC (room temperature).

Do not refrigerate or freeze.

Store in the original container, in order to protect from light.

The suspension should be discarded if not administered immediately after reconstitution with the sterile diluent.

6.5 Nature and contents of container

LUCRIN DEPOT 3,75 mg PDS is available in a single dose prefilled dual-chambered syringe containing sterile lyophilised microspheres of leuprolide acetate (3,75 mg) and 1 mL of diluent for suspension for injection. The dual-chambered syringe consists of a glass cartridge, rubber stopper, the front assembly of the syringe, the finger grip and the plunger rod. The syringe is a colourless silicone-baked cartridge of highly resistant borosilicate glass (Type I glass), with siliconized chlorobutyl rubber stoppers and a stainless steel 25 gauge needle.

LUCRIN DEPOT 3,75 mg PDS is a white powder. The sterile liquid for reconstitution is a clear, colourless liquid. After reconstitution the suspension should appear milky.

6.6 Special precautions for disposal and other handling

Reconstitution

The lyophilised microspheres are to be reconstituted and administered monthly as a single intramuscular or subcutaneous injection in accordance with the following directions:

1. Screw the white plunger into the back stopper until the stopper begins to turn.
2. Remember to screw the luer lock mechanism tight by twisting the needle clockwise until it is tight. Do not over tighten the needle.
3. Hold the syringe UPRIGHT and release the diluent by SLOWLY PUSHING (6 to 8 seconds) until the front stopper reaches the blue line in the middle of the shaft.
4. Gently mix the microspheres (particles) to thoroughly mix the particles with the diluent, until a uniform suspension is obtained. The suspension will have a milky appearance.
5. If the particles continue to adhere to the stopper, tap the syringe with your finger.

6. Remove the protective cap positioned over the needle, and expel air from the syringe by depressing the plunger.
7. Inject the entire contents of the syringe either intramuscularly or subcutaneously at the time of reconstitution, in the same way as you would give a normal injection. The suspensions settles very quickly following reconstitution; therefore, LUCRIN DEPOT 3,75 mg PDS should be mixed and used immediately.

NOTE: Aspirated blood would be visible just below the luer lock if a blood vessel is accidentally penetrated.

The injection sites should be varied, periodically.

Although the solution has been shown to be stable for 24 hours following reconstitution, since the product does not contain preservatives, the suspension should be discarded if not used immediately.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

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South Africa

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 October 2025

10 DATE OF REVISION OF THE TEXT