SCHEDULING STATUS

S4

1 NAME OF MEDICINE

LUCRIN DEPOT 11,25 – Lyophilised microspheres for injection

LUCRIN DEPOT DILUENT – Sterile diluent for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LUCRIN DEPOT 11,25: Each single-dose vial contains leuprolide acetate 11,25 mg

Contains mannitol (sugar-alcohol)

For full lists of excipients, see section 6.1

LUCRIN DEPOT DILUENT: Each 2 mL ampoule of diluent for injection contains mannitol, polysorbate 80, sodium carboxymethylcellulose and water for injection.

3 PHARMACEUTICAL FORM

LUCRIN DEPOT 11,25 – Lyophilised microspheres for injection

LUCRIN DEPOT DILUENT – Sterile diluent for injection

4 CLINICAL PARTICULARS

LUCRIN DEPOT 11,25 is indicated in:

4.1 Therapeutic indications

Prostate Cancer

LUCRIN DEPOT 11,25 is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchidectomy or oestrogen administration is either not indicated or unacceptable to the patient.

Endometriosis

LUCRIN DEPOT 11,25 is indicated in the treatment of endometriosis for a period of six months. It can be used as sole therapy or as an adjunct to surgery.

Uterine Fibroids

LUCRIN DEPOT 11,25 is indicated in the treatment of leiomyoma uteri (uterine fibroids) for a period up to six months. Therapy may be preoperative prior to myomectomy or hysterectomy, or it may provide symptomatic relief for the perimenopausal woman who does not desire surgery.

Breast Cancer

LUCRIN DEPOT 11,25 is indicated as adjuvant therapy to surgery in breast carcinomas.

4.2 Posology and method of administration

General

LUCRIN DEPOT 11,25 must be administered under the supervision of a medical practitioner.

Prostate Cancer

The recommended dose of LUCRIN DEPOT 11,25 in the palliative treatment of advanced prostatic carcinoma is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

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.

Endometriosis/Uterine Fibroids

The recommended dose of LUCRIN DEPOT 11,25 in the treatment of endometriosis and uterine fibroids is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

Breast Cancer

The recommended dose of LUCRIN DEPOT 11,25 as adjuvant therapy to surgery in breast carcinoma is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

4.3 Contraindications

LUCRIN DEPOT 11,25 is contraindicated in patients with known hypersensitivity to leuprolide acetate or similar nonapeptides or any of the excipients. (see section 6.1)

LUCRIN DEPOT 11,25 is contraindicated in women who are, or may become pregnant while receiving the medicine.

LUCRIN DEPOT 11,25 should not be administered to women who are breastfeeding.

LUCRIN DEPOT 11,25 should not be administered to patients with undiagnosed vaginal bleeding.

LUCRIN DEPOT should not be administered to patients who have had an anaphylactic reaction to leuprolide acetate (see section 4.4).

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 11,25. 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.

Isolated cases of anaphylaxis have been reported with the monthly depot formulation (LUCRIN DEPOT 3,75) of leuprolide acetate.

Convulsions

Postmarketing reports of convulsions have been observed in patients on LUCRIN DEPOT 11,25 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.

Men

Prostate Cancer

Worsening of signs and symptoms of prostate cancer have been reported during the first week of treatment with LUCRIN DEPOT 11,25. Patients may experience a temporary increase in bone pain, which may be managed symptomatically. Cases of ureteral obstruction and spinal cord compression have been observed, which may cause paralysis with or without fatal complications. For patients at risk, the medical practitioner may consider initiating therapy with daily injections of a GnRH agonist 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 11,25. 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 11,25, 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 such as LUCRIN DEPOT 11,25 in men. The risk should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving LUCRIN DEPOT 11,25 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 medicines that might prolong the QT interval medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating LUCRIN DEPOT 11,25.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of LUCRIN DEPOT 11,25 with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de points 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.

Women

Endometriosis/Uterine Fibroids

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the medicine.

Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy at adequate doses. However, reports of heavy vaginal bleeding requiring medical or surgical intervention with continued therapy have been reported in the treatment of submucous leiomyoma uteri.

LUCRIN DEPOT 11,25 is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used.

Changes in Bone Density

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 pre-treatment 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 11,25 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.

Changes in Laboratory Values During Treatment

- *Liver Enzymes*

Three percent of uterine fibroid patients treated with LUCRIN DEPOT 11,25, experienced transaminase values that were at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

- *Lipids*

Triglycerides were increased above the upper limit of normal in 32 % of the endometriosis patients who received LUCRIN DEPOT 11,25. Of those endometriosis and uterine fibroid patients whose pre-treatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in endometriosis patients and +11 mg/dL to +29 mg/dL in uterine fibroid patients. In the endometriosis treated patients, increases from the pre-treatment values were statistically significant (p<0,03).

Prostate Cancer

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 and/or urinary obstruction or haematuria which, if aggravated, may lead to temporary weakness, paralysis or paresthesia of the lower limbs or worsening of urinary symptoms.

Impairment of fertility

Studies in adults with LUCRIN DEPOT 11,25 have shown full reversibility of fertility suppression when the medicine is discontinued after continuous administration for periods of up to 24 weeks.

4.5 Interaction with other medicines and other forms of interaction

Medicine interactions

Pharmacokinetic-based medicine-medicine interaction studies have not been conducted with LUCRIN DEPOT 11,25. However, due to leuprolide acetate 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.

Laboratory Tests

Response to LUCRIN DEPOT 11,25 used in the palliative treatment of advanced prostatic cancer, should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were reached within two to four weeks and once achieved was maintained for as long as the patients received their injections.

Medicine/Laboratory Test Interactions

Administration of LUCRIN DEPOT 11,25 in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after LUCRIN DEPOT 11,25 treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUCRIN DEPOT 11,25 may be misleading.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of LUCRIN DEPOT 11,25 in pregnancy has not been established.

Breastfeeding

It is not known whether LUCRIN DEPOT 11,25 is excreted in human milk. Therefore LUCRIN DEPOT 11,25 should not be administered to women breastfeeding their infants.

4.7 Effects on ability to drive and use machines

LUCRIN DEPOT 11, 25 may cause convulsion, blurred vision and dizziness which may affect the ability to drive and use machines (see section 4.8)

4.8 Undesirable effects

Prostate Cancer

The following adverse events 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 disorder, cold sweat, hirsutism
Reproductive system and breast disorders	Gynaecomastia, breast tenderness, erectile

	dysfunction, testicular pain, breast enlargement, breast pain, prostate pain, penile swelling, penis disorder, 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 increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week 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 paresthesia of the lower limbs or worsening of urinary symptoms (see section 4.4).

Table 1 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 1: ADVERSE EVENTS REPORTED IN PROSTATE CANCER CLINICAL STUDIES

System Organ Class	Frequency	Adverse Events
Infections and infestations	Common	Bronchitis, urinary tract infection
	Uncommon	Infected cyst, viral infection, candidiasis, sepsis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Pseudolymphoma
Blood and lymphatic system disorder	Common	Anaemia
	Uncommon	Eosinophilia
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very Common	Abnormal weight gain
	Common	Anorexia, abnormal loss of weight
	Uncommon	Hyperglycaemia, hypoglycaemia, dehydration
Psychiatric disorders	Very Common	Libido decreased
	Common	Insomnia, depression
Nervous system disorders	Common	Headache, paraesthesia
	Uncommon	Dizziness, somnolence, tremor, simple partial seizures
Cardiac disorders	Uncommon	Angina pectoris, cardiac failure, bradycardia, atrioventricular block
Vascular disorders	Very Common	Hot flush
	Common	Lymphoedema, hypertension, thrombophlebitis
	Uncommon	Aneurysm, circulatory collapse, flushing, haematoma

System Organ Class	Frequency	Adverse Events
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, asthma
	Uncommon	Cough, chronic obstructive pulmonary disease
Gastrointestinal disorders	Common	Constipation, nausea
	Uncommon	Gastritis
Hepato-biliary disorder	Uncommon	Hepatitis cholestatic, hepatocellular injury
Skin and subcutaneous tissue disorder	Very Common	Hyperhidrosis
	Common	Pruritus
	Uncommon	Alopecia, rash, dry skin
Musculoskeletal, connective tissue and bone disorders	Very Common	Bone pain
	Common	Arthralgia, back pain, pain in extremity, muscular weakness
	Uncommon	Myalgia, muscle spasms
Renal and urinary disorders	Very Common	Nocturia
	Common	Dysuria, haematuria
	Uncommon	Urinary incontinence, pollakiuria, urinary retention, micturition disorder
Reproductive system and breast disorders	Very Common	Erectile dysfunction, testicular disorder
	Common	Gynaecomastia
General disorders and administration site conditions	Very Common	Fatigue, injection site reaction
	Common	Pain, oedema peripheral, asthenia, injection site mass, injection site pain,

System Organ Class	Frequency	Adverse Events
		influenza like illness, application site oedema
	Uncommon	Chest pain, gravitational oedema, mucosal dryness, malaise, gait disturbance
Investigations	Common	Prostatic specific antigen increased, blood alkaline phosphatase increased, blood lactic dehydrogenase increased, alanine aminotransferase increased/ALT, aspartate aminotransferase increased/AST, gamma-glutamyltransferase increased, electrocardiogram abnormal
	Uncommon	Red blood cell sedimentation rate increased, blood testosterone increased
Injury, poisoning and procedural complications	Uncommon	Fracture, head injury, fall, device occlusion
Surgical and medical procedures	Uncommon	Tumor excision, transurethral bladder resection, lithotripsy

Women:

The following adverse events are commonly 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, seborrhea, 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, galactorrhea, 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 11,25. 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 11,25 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 2 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, uterine fibroid 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 ischemic 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 2: ADVERSE EVENTS REPORTED IN ENDOMETRIOSIS, UTERINE FIBROIDS AND BREAST CANCER CLINICAL STUDIES

System Organ Class	Preferred Term	Endometriosis	Uterine fibroids	Breast Cancer
Infections and infestations	Infection	Uncommon		
	Rhinitis		Uncommon	
	Upper respiratory tract infection			Uncommon
	Pyelonephritis	Uncommon		
	Furuncle	Uncommon		
	Vulvovaginal candidiasis		Uncommon	
	Influenza		Uncommon	
	Nasopharyngitis			Very Common[a]
Blood and lymphatic system disorder	Leukopenia			Uncommon
Metabolism and nutrition disorders	Anorexia	Uncommon		Uncommon
	Diabetes mellitus	Common[b]	Common[b]	Common[b]
	Appetite Increased	Uncommon	Uncommon	Very common
	Appetite Decreased			Common
	Hypercholesterolaemia	Common		
	Abnormal weight gain	Very common	Common	Very common
	Abnormal loss of weight	Common	Common	Very common

Psychiatric disorders	Affect lability	Very common	Common	
	Mood swings[a]			Very common
	Personality disorder	Uncommon		
	Nervousness	Very common	Common	Very common
	Decreased libido	Very common	Common	
	Loss of libido	Common	Common	Common
	Libido increased	Common	Common	Common
	Insomnia	Very common	Common	Very common
	Sleep disorder			Common
	Depression[a]	Very common	Common	Very common
	Major depression	Common		
	Anxiety	Common	Uncommon	
	Delusion	Uncommon		
	Thinking abnormal	Uncommon		
	Confusional state	Common		
	Euphoric mood	Uncommon		
	Hostility	Common		
	Apathy	Uncommon		
	Nervousness/anxiety	Very common		
Nervous system disorders	Dizziness	Very common	Common	Very common[c]
	Dizziness postural			Common
	Headache	Very common	Very common	Very common[d]

	Paraesthesia	Common	Common	Common
	Somnolence	Uncommon		Common
	Memory impairment			Common
	Amnesia	Uncommon		
	Dysgeusia		Uncommon	
	Hypoaesthesia			Common
	Syncope	Uncommon		
	Migraine	Common	Uncommon	
	Hypertonia	Common	Common	
	Ataxia	Uncommon		
	Tremor			Common
Eye disorders	Eye disorder	Uncommon		
	Visual impairment	Common		
	Amblyopia	Common		
	Eye pain	Uncommon		
	Conjunctivitis		Uncommon	Common
Ear and labyrinth disorders	Vertigo	Common		
	Deafness			Common
	Motion sickness			Common
	Auricular swelling			Common
Cardiac disorders	Tachycardia	Uncommon	Uncommon	
	Palpitations	Common		Common

Vascular disorders	Hot flush	Common	Common	Very common
	Vasodilatation	Very common	Very common	Common
	Hypotension	Common	Common	Common
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon		Common
	Dyspnoea			Common
	Dysphonia	Uncommon		
	Sputum increased			Common
	Cough			Common
Gastrointestinal disorders	Constipation	Common	Uncommon	Common
	Nausea	Very common	Common	Very common[d]
	Vomiting		Uncommon	Common
	Nausea and vomiting	Common	Uncommon	
	Abdominal distention	Uncommon		Common
	Diarrhoea	Common	Common	Common
	Gingivitis			Common
	Dyspepsia	Uncommon		
	Flatulence	Uncommon	Common	
	Gastritis	Uncommon		Common
	Gingival bleeding	Uncommon		
	Dry mouth	Common	Uncommon	
	Abdominal pain	Common	Common	

	Abdominal pain upper			Common
	Abdominal pain lower			Common
	Stomatitis			Common
	Retching			Common
Hepatobiliary disorder	Liver tenderness	Uncommon		
	Hepatic function abnormal			Common
	Hepatic steatosis			Common
Skin and subcutaneous tissue disorders	Erythema			Common
	Alopecia	Common		Common
	Ecchymosis	Common		
	Acne	Very common	Common	Common
	Seborrhoea	Common	Common	Common
	Rash	Common	Common	Common
	Rash maculo-papular	Uncommon		
	Dry skin	Common	Common	Common
	Photosensitivity reaction	Uncommon		
	Urticaria	Common	Common	Common
	Skin odour abnormal	Common	Uncommon	Common
	Hyperhidrosis	Common	Common	Very common[d]
	Hair growth abnormal	Common	Common	Common
	Hirsutism	Common	Uncommon	Common

	Hair disorder	Uncommon	Common	Common
	Eczema	Common	Common	Common
	Nail disorder	Common	Uncommon	Common
	Skin discolouration		Uncommon	
	Night sweats	Common	Common	Common
	Dermatitis bullous		Uncommon	
	Dermatitis			Very Common[a]
Musculoskeletal and connective tissue disorders	Bone pain			Common
	Myalgia	Uncommon	Uncommon	
	Arthropathy	Common	Common	
	Arthralgia	Common	Common	Very common
	Back pain	Common	Common	Very common
	Osteoarthritis			Common
	Arthritis	Uncommon		
	Nuchal rigidity	Common		
	Neck pain	Common		Common
	Muscular weakness			Common
	Musculoskeletal stiffness			Common
	Muscle twitching			Common
Renal and urinary disorders	Urinary incontinence	Uncommon		
	Dysuria	Common		
	Pollakiuria	Uncommon		Common

Reproductive system and breast disorders	Vaginal haemorrhage	Common	Common	Common
	Dysmenorrhea	Common	Common	Common
	Menstrual disorder	Common	Uncommon	Common
	Breast enlargement	Uncommon	Common	Common
	Breast engorgement	Uncommon	Common	Common
	Breast atrophy	Common	Common	Common
	Genital discharge	Common	Common	Common
	Vaginal discharge	Common	Common	Common
	Galactorrhoea	Uncommon	Common	Common
	Breast pain	Common	Common	Common
	Pelvic pain	Common	Uncommon	
	Metrorrhagia	Common	Uncommon	Common
	Menopausal symptoms	Common	Common	Common
	Dyspareunia	Common	Common	Common
	Uterine disorder	Common	Common	Common
	Vulvovaginitis	Very common	Very common	Common
	Menorrhagia	Common	Uncommon	Common
General disorders and administration site conditions	Pain	Common	Common	
	Chest pain	Common	Uncommon	Common
	Oedema	Common	Uncommon	Common
	Oedema peripheral	Common	Common	Common
	Face oedema	Uncommon		

	Generalised oedema	Uncommon		
	Asthenia	Common	Common	Very common
	Fatigue			Common
	Pyrexia			Common[c]
	Injection site reaction	Uncommon		Common
	Injection site mass	Uncommon	Uncommon	
	Injection site pain	Common	Common	Very common[d]
	Injection site induration			Very common[d]
	Injection site pruritus			Common
	Injection site erythema			Common
	Chills	Common	Common	
	Injection site hypersensitivity	Uncommon		
	Thirst	Common		
	General physical health deterioration			Very common
	Feeling hot	Common	Common	Very common[d]
	Irritability	Common	Common	Common
	Malaise			Common
	Condition aggravated		Uncommon	
Investigations	Bone Density Decreased	Common	Common	Common
	Glucose tolerance impaired	Common[b]	Common[b]	Common[b]

	Total cholesterol increased	Common[b]	Common[b]	Common[b]
	LDL increased	Common[b]	Common[b]	Common[b]
	Triglycerides increased[b]	Common	Common[b]	Common[b]
	Osteoporosis[b]	Common	Common[b]	Common[b]
	Body temperature increased			Uncommon
	Occult blood positive			Common
	Liver function test abnormal		Common	
	Laboratory test abnormal		Uncommon	
Injury, poisoning and procedural complications	Procedural pain			Common
[a] In Breast Cancer Patients treated with LUCRIN DEPOT 11,25 and Tamoxifen the frequency was reported as Very Common				
[b] Long term exposure (6-12 months)				
[c] In Breast Cancer Patients treated with LUCRIN DEPOT 11,25 and Tamoxifen the frequency was reported as Common				
[d] Frequency for this PT was Very Common in both the LUCRIN only arm and in the LUCRIN plus Tamoxifen clinical trials				

Post-Marketing Surveillance

TABLE 3: ADVERSE EVENTS SEEN IN POST-MARKETING EXPERIENCE FOR PROSTATE CANCER, ENDOMETRIOSIS, FIBROIDS AND BREAST CANCER POPULATION

System Organ Class	Adverse Events
Infections and infestations	Infection
	Urinary tract infection
	Pharyngitis
	Pneumonia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Skin cancer
	Anaemia
Immune system disorders	Anaphylactic reaction
Endocrine disorders	Goiter
	Pituitary apoplexy
Metabolism and nutrition disorders	Diabetes mellitus
	Increased appetite
	Hypoglycaemia
	Dehydration
	Hyperlipidaemia
	Hyper-phosphataemia
	Hypoproteinaemia
Psychiatric disorders	Mood swings[a]
	Nervousness
	Libido increased

System Organ Class	Adverse Events
	Insomnia
	Sleep disorder
	Depression[a]
	Anxiety
	Delusion
	Suicidal ideation
	Suicide attempt
Nervous system disorders	Dizziness
	Headache
	Paraesthesia
	Lethargy
	Memory impairment
	Dysgeusia
	Hypoaesthesia
	Syncope
	Neuropathy peripheral
	Cerebrovascular accident
	Loss of consciousness
	Transient ischemic attack
	Paralysis
	Neuromyopathy
	Convulsion

System Organ Class	**Adverse Events**
Eye disorders	Vision blurred
	Eye disorder
	Visual impairment
	Amblyopia
	Dry eye
Ear and labyrinth disorders	Tinnitus
	Hearing impaired
Cardiac disorders	Cardiac failure congestive
	Dysrhythmia
	Myocardial infarction
	Angina pectoris
	Tachycardia
	Bradycardia
	Sudden cardiac death
Vascular disorders	Lymphoedema
	Hypertension
	Phlebitis
	Thrombosis
	Hypotension
	Varicose vein
Respiratory, thoracic and mediastinal disorders	Pleural rub
	Pulmonary fibrosis

System Organ Class	Adverse Events
	Epistaxis
	Dyspnoea
	Haemoptysis
	Cough
	Pleural effusion
	Lung infiltration
	Respiratory disorder
	Sinus congestion
	Pulmonary embolism
	Interstitial lung disease
Gastro-intestinal disorders	Constipation
	Nausea
	Vomiting
	Gastrointestinal haemorrhage
	Abdominal distention
	Diarrhoea
	Dysphagia
	Dry mouth
	Duodenal ulcer
	Gastrointestinal disorder
	Peptic ulcer
	Rectal polyp

System Organ Class	**Adverse Events**
Hepato-biliary disorder	Hepatic function abnormal
	Serious liver injury
	Jaundice
Skin and subcutaneous tissue disorders	Alopecia
	Ecchymosis
	Rash
	Dry skin
	Photosensitivity reaction
	Urticaria
	Dermatitis
	Hair growth abnormal
	Pruritus
	Pigmentation disorder
	Skin lesion
Musculo-skeletal and connective tissue disorders	Myalgia
	Bone swelling
	Arthropathy
	Arthralgia
	Ankylosing spondylitis
	Tenosynovitis
Renal and urinary disorders	Urinary incontinence
	Pollakiuria

System Organ Class	Adverse Events
	Micturition urgency
	Haematuria
	Bladder spasm
	Urinary tract disorder
	Urinary tract obstruction
Reproductive system and breast disorders	Gynaecomastia
	Vaginal haemorrhage
	Menstrual disorder
	Metrorrhagia
	Breast tenderness
	Testicular atrophy
	Testicular pain
	Breast pain
	Testicular disorder
	Penile swelling
	Penis disorder
	Prostatic pain
General disorders and administration site conditions	Pain
	Oedema
	Asthenia
	Pyrexia
	Injection site reaction

System Organ Class	Adverse Events
	Injection site inflammation
	Injection site pain
	Injection site induration
	Injection site abscess sterile
	Injection site haematoma
	Chills
	Nodule
	Thirst
	Inflammation
	Pelvic fibrosis
Investigations	Increased blood urea
	Increased blood uric acid
	Increased blood creatinine
	Increased blood calcium
	Abnormal electrocardiogram
	ECG signs of myocardial ischemia
	Abnormal liver function test
	Decreased platelet count
	Decreased blood potassium
	Increased white blood cell count
	Decreased white blood cell count
	Blood thromboplastin decreased

System Organ Class	Adverse Events
	Prolonged prothrombin time (increased INR)
	Prolonged activated partial thromboplastin time
	Cardiac murmur
	Increased low density lipoprotein
	Increased blood triglycerides
	Increased blood bilirubin
Injury, poisoning and procedural complications	Spinal fracture

Reporting of side effects

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 asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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

4.9 Overdose

See "section 4.4 and section 4.8". In cases of overdosage, the patients should be monitored closely and treatment should be 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). The analogue possesses greater potency than the natural hormone.

Leuprolide acetate is a potent inhibitor of gonadotropin secretion. Following an initial stimulation chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroideogenesis.

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 esterone 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 castrate or prepubertal levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating leuprolide acetate therapy at recommended doses.

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.

5.2 Pharmacokinetic properties

Leuprolide acetate is not active when given orally. The bioavailability following subcutaneous administration is comparable to that after intramuscular administration.

Absorption

Following a single administration of leuprolide acetate depot suspension 11,25 mg in males with advanced prostate cancer, a rapid increase of leuprolide acetate concentration was observed. A mean peak leuprolide plasma concentration of 21,82 (± 11,24) ng/mL was observed three hours after injection. Leuprolide acetate reached plateau levels within 7 to 14 days after injection. At week four, a mean leuprolide plasma concentration of 0,26 (± 0,10) ng/mL was noted. It then declined to a mean leuprolide plasma concentration of 0,17 (± 0,18) ng/mL at 12 weeks.

Following a single intramuscular injection of leuprolide acetate depot suspension 11,25 mg in female subjects, a mean plasma leuprolide concentration of 36,3 ng/mL was observed at four hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean level then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide concentration from 3 to 12 weeks was 0,23 ± 0,09 ng/mL.

Distribution

The mean-steady-state volume of distribution of leuprolide following 1 mg 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 14C-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LUCRIN DEPOT 11,25 Lyophilised microspheres for injection:

Polyactic acid

Mannitol

6.2 Incompatibilities

No other fluid should be used for reconstitution of LUCRIN DEPOT 11,25.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature (below 25 ºC).

6.5 Nature and contents of container

LUCRIN DEPOT 11,25 is available in a single dose administration kit containing one vial of sterile lyophilised microspheres of leuprolide acetate (11,25 mg); one ampoule of diluent, one syringe with two 23-gauge needles and one alcohol swab.

LUCRIN DEPOT 11,25 is sterile lyophilised microspheres, which when mixed with Lucrin Depot Diluent, becomes a milky white suspension.

6.6 Special precautions for disposal and other handling

Preparation for Administration

The vial of LUCRIN DEPOT 11,25 should be reconstituted immediately prior to administration in accordance with the following directions:

1. Using a syringe with a 23-gauge needle, withdraw 2 mL of diluent from the ampoule, and inject it into the vial of LUCRIN DEPOT 11,25 using aseptic technique.
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution

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 a preservative, the suspension should be discarded if not used immediately.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof

1709

8. REGISTRATION NUMBER

LUCRIN DEPOT 11,25 : 32/21.10/0317

LUCRIN DEPOT DILUENT : 27/34/0371

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 March 2000

10. DATE OF REVISION OF THE TEXT

23 August 2022