Prescribing Information

NAME OF THE MEDICINAL PRODUCT

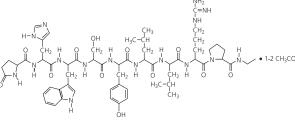
Lucrin[®] PDS Depot 11.25 mg

(Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg)

DESCRIPTION

Leuprorelin acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LHRH). The analogue possesses greater potency than the natural hormone.

The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Dleucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) and the structural formula is as follows:



Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is a formulation of leuprorelin acetate supplied as lyophilized microspheres. When mixed with diluent, it becomes a suspension which is administered as an intramuscular or subcutaneous injection every three months.

Active/Inactive Ingredients

Leuprorelin Acetate Depot Suspension - 3 Month 11.25 mg contains leuprorelin acetate (11.25 mg), a polymer polylactic acid (99.3 mg) and mannitol (19.45 ma)

During the manufacture of Leuprorelin Acetate for Depot Suspension 11.25 mg, acetic acid is lost, leaving the peptide.

The diluent used for reconstitution with the leuprorelin acetate powder is a clear, colorless, slightly viscous solution of carboxymethylcellulose sodium, mannitol polysorbate 80, water for injection and glacial acetic acid to control pH. The compound is easily soluble in polar solutions such as water and anhydrous

ethanol and propylene glycol. It is nearly insoluble in chloroform. The pH value of a solution containing 100 mg dry powder of leuprorelin acetate in one mL of solution is approximately 5 to 7

PHARMACOLOGIC PROPERTIES

Pharmacodynamic Properties

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 tumors (prostatic tumors in Nobel and Dunning male rats and DMBA-induced mammary tumors in female rats), as well as atrophy of the reproductive organs.

In humans, administration of leuprorelin acetate results in an initial increase in circulating levels of luteinizing 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 leuprorelin acetate results in decreased levels of LH and FSH and sex steroids. In males, testosterone is reduced to castrate or pre-pubertal levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating drug therapy at recommended doses.

Pharmacokinetic Properties

Leuprorelin acetate is not active when given orally. Bioavailability of this agent following subcutaneous administration is comparable to that after intramuscular administration.

Absorption

Following a single administration of Leuprorelin Acetate Depot Suspension -3 Month 11.25 mg in males with advanced prostate cancer, a rapid increase of leuprorelin acetate concentration was observed. A mean peak leuprorelin plasma concentration of 21.82 (± 11.24) ng/mL was observed three hours

after injection. Leuprorelin acetate reached plateau levels within 7 to 14 days after injection At week 4, a mean leuprorelin plasma concentration of $0.26 (\pm 0.10)$ ng/mL was noted. It then declined to a mean leuprorelin plasma concentration of 0.17 (± 0.08) ng/mL at 12 weeks.

Following a single injection of the three-month formulation of Leuprorelin Acetate Depot Suspension 11.25 mg in healthy females, a mean plasma leuprorelin concentration of 36.3 ng/mL was observed at 4 hours. Leuprorelin 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) leuprorelin concentration from 3 to 12 weeks was 0.23 \pm 0.09 ng/mL However, intact leuprorelin and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

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%.

WARNINGS AND PRECAUTIONS

All Populations

As the effect of Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is present throughout the course of therapy, the drug should only be used in patients who require hormonal suspension for at least three months. During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an

increase in clinical signs and symptoms may be observed (see **PHARMACOLOGIC PROPERTIES**)

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 Safe use of leuprorelin acetate in pregnancy has not been established clinically

Before starting treatment with leuprorelin acetate, it is advisable to establish whether the patient is pregnant. Leuprorelin acetate is not a contraceptive If contraception is required, a nonhormonal method of contraception should be used

Bone Mineral Density

Bone mineral density changes can occur during any hypoestrogenic state in women and in long-term use in prostate cancer in men. There is no data in men regarding reversibility after withdrawal of leuprorelin acetate. In women bone mineral density loss may be reversible after withdrawal of leuprorelin acetate (see ADVERSE REACTIONS, Women).

Convulsions

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

Prostate Cancer

Men

Initially, leuprorelin acetate, like other LH-RH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer may occasionally develop during the first few weeks of leuprorelin acetate for depot suspension treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteric obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. For patients at risk, initiation of therapy with daily leuprorelin acetate injection for the first two weeks to facilitate withdrawal of treatment may be considered. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Hyperglycemia and an increased risk of developing diabetes have been reported n men receiving GnRH agonists. Hyperglycemia may represent development o diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving GnRH agonists, and manage with current practice for treatment of hyperglycemia or diabetes.

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with 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

Laboratory Tests

Response to leuprorelin acetate should be monitored by measuring serum levels of testosterone, as well as prostate specific antigen. 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 of treatment. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections on time

Endometriosis/Uterine Fibroids

Women

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the drug. 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, heavy vaginal bleeding requiring medical or surgical intervention with continued therapy have been reported in the treatment of submucous leiomyoma. Safe use of leuprorelin acetate in pregnancy has not been established clinically

Before starting treatment with leuprorelin acetate, it is advisable to establish whether the patient is pregnant. Leuprorelin acetate is not a contraceptive. If contraception is required, a

non'hormonal method of contraception should be used.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted

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, hyperhidrosis, hair growth abnormal, hirsutism, hair disorder, eczema, nail disorder, night sweats

Reproductive system and breast disorders: vaginal haemorrhage. dysmenorrhea, 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.

Clinical and Post-marketing

The following sections present adverse reactions seen in clinical studies or post-marketing experience. They are arranged by patient populations: Men,

Prostate Cancer

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 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 paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS AND PRECAUTIONS**). Table 1 presents all adverse drug reactions (ADR) and frequencies (very common [\geq 1/10]; common [\geq 1/100 to <1/10]; uncommon [\geq 1/1,000 to <1/100]; not known [unable to estimate frequency based upon available data]) from prostate

cancer clinical studies and post-marketing experience. A blank indicates that the ADR was not seen from that particular source. As leuprorelin acetate has multiple indications, and therefore patient populations. some of these post-marketing adverse reactions may not be applicable to

every patient. For a majority of these adverse reactions, a cause and effect relationship has not been established.

Table 1: Prostate Cancer

		Prostate Cancer 11.25 mg/3 month	Post-Marketing		
System Organ Class	Preferred Term	11.25 mg/3 month Frequency	Frequency		
Infections and	Infection		Not known		
infestations	Bronchitis	Common			
	Urinary tract infection Infected cyst	Common Uncommon	Not known		
	Viral infection	Uncommon			
	Candidiasis	Uncommon			
	Sepsis	Uncommon	Not known		
	Pharyngitis Pneumonia		Not known		
Neoplasms benign, malignant and	Pseudolymphoma	Uncommon			
unspecified (incl cysts and polyps)	Skin cancer		Not known		
Blood and lymphatic	Anaemia	Common	Not known		
system disorders	Eosinophilia	Uncommon			
lmmune system disorders	Hypersensitivity Anaphylactic reaction	Uncommon	Net luce au un		
Endocrine disorders	Goiter		Not known Not known		
	Pituitary apoplexy		Not known		
Metabolism and nutrition disorders	Anorexia	Common			
	Diabetes mellitus Increased appetite		Not known Not known		
	Hyperglycaemia	Uncommon			
	Hypoglycaemia	Uncommon	Not known		
	Dehydration Hyperlipidaemia	Uncommon	Not known Not known		
	Hyperphosphataemia		Not known		
	Hypoproteinaemia		Not known		
	Abnormal weight gain	Very common			
	Abnormal loss of	Common			
Psychiatric disorders	weight Mood swingsª		Not known		
	Nervousness		Not known		
	Libido decreased	Very common			
	Libido increased	Common	Not known		
	Insomnia Sleep disorder	Common	Not known Not known		
	Depression ^a	Common	Not known		
	Anxiety		Not known		
	Delusion Suicidal ideation		Not known Not known		
	Suicidal attempt		Not known		
Nervous system disorders	Dizziness	Uncommon	Not known		
uisorders	Headache	Common	Not known		
	Paraesthesia Lethargy	Common	Not known Not known		
	Somnolence	Uncommon			
	Memory impairment		Not known		
	Dysgeusia		Not known		
	Hypoaesthesia Syncope		Not known Not known		
	Tremor	Uncommon			
	Simple partial seizures	Uncommon			
	Neuropathy peripheral Cerebrovascular		Not known Not known		
	accident				
	Loss of consciousness Transient ischemic		Not known Not known		
	attack				
	Paralysis		Not known		
	Neuromyopathy Convulsion		Not known Not known		
Eye disorders	Vision blurred		Not known		
	Eye disorder		Not known		
	Visual impairment		Not known Not known		
	Amblyopia Dry eye		Not known Not known		
Ear and labyrinth	Tinnitus		Not known		
disorders	Hearing impaired		Not known		
Cardiac disorders	Cardiac failure congestive		Not known		
	congestive				
	Arrhythmia		Not known		
	Arrhythmia Myocardial infarction	Uncommon	Not known		
	Arrhythmia	Uncommon			
	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure	Uncommon Uncommon	Not known Not known Not known		
	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia		Not known Not known Not known Not known		
	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death	Uncommon Uncommon	Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia	Uncommon	Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema	Uncommon Uncommon Uncommon Very common Common	Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension	Uncommon Uncommon Uncommon Very common Common Common	Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema	Uncommon Uncommon Uncommon Very common Common	Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis	Uncommon Uncommon Uncommon Very common Common Common	Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm	Uncommon Uncommon Very common Common Common Common Uncommon	Not known Not known Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon	Not known Not known Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known Not known Not known Not known Not known Not known Not known		
Vascular disorders	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon	Not known Not known Not known Not known Not known Not known Not known Not known		
	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough Asthma	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Common	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough Asthma Chronic obstructive pulmonary disease	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon	Not known Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough Asthma Chronic obstructive pulmonary disease Pleural effusion	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Common	Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough Asthma Chronic obstructive pulmonary disease Pleural effusion Lung infiltration	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Common	Not known		
Respiratory, thoracic and mediastinal	Arrhythmia Myocardial infarction Angina pectoris Tachycardia Cardiac failure Bradycardia Sudden cardiac death Atrioventricular block Hot flush Lymphoedema Hypertension Thrombophlebitis Phlebitis Thrombosis Aneurysm Circulatory collapse Flushing Haematoma Hypotension Varicose vein Pleural rub Pulmonary fibrosis Epistaxis Dyspnoea Haemoptysis Cough Asthma Chronic obstructive pulmonary disease Pleural effusion	Uncommon Uncommon Very common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Common	Not known		

System Organ Class		Prostate Cancer 11.25 mg/3 month Frequency	Post-Marketing Frequency Not known
Gastrointestinal disorders	Constipation Nausea	Common Common	Not known Not known
	Vomiting Gastritis	Uncommon	Not known
	Gastrointestinal haemorrhage Abdominal distention		Not known Not known
	Diarrhea Dysphagia		Not known Not known
	Dry mouth Duodenal ulcer		Not known Not known
	Gastrointestinal disorder Peptic ulcer		Not known Not known
Hepato-biliary	Rectal polyp Hepatic function		Not known Not known
disorders	abnormal Hepatitis cholestatic	Uncommon	
	Hepatocellular injury Serious liver injury	Uncommon	Not known
Skin and subcutaneous tissue	Jaundice Alopecia Ecchymosis	Uncommon	Not known Not known Not known
disorders	Ecchymosis Rash Dry skin	Uncommon Uncommon	Not known Not known Not known
	Dry skin Photosensitivity reaction		Not known Not known
	Urticaria Hyperhidrosis	Very common	Not known
	Dermatitis Hair growth abnormal		Not known Not known
	abnormal Pruritus Pigmentation disorder	Common	Not known Not known
Musculoskeletal and	Skin lesion Bone pain	Very common	Not known
connective tissue disorders	Myalgia Bone swelling	Uncommon	Not known Not known
	Arthropathy Arthralgia	Common	Not known Not known
	Back pain Muscular weakness	Common Common	
	Pain in extremity Muscle spasms	Common Uncommon	
	Ankylosing spondylitis Tenosynovitis		Not known Not known
Renal and urinary disorders	Urinary incontinence Dysuria	Uncommon Common	Not known
	Pollakiuria Micturition urgency	Uncommon	Not known Not known
	Haematuria Nocturia	Common Very common	Not known
	Urinary retention Micturition disorder Bladder spasm	Uncommon Uncommon	Not known
	Bladder spasm Urinary tract disorder Urinary tract		Not known Not known Not known
Reproductive system	obstruction Gynaecomastia	Common	Not known
and breast disorders	Breast tenderness Erectile dysfunction	Very common	Not known
	Testicular atrophy Testicular pain		Not known Not known
	Breast pain Testicular disorder	Very common	Not known Not known
	Penile swelling Penis disorder		Not known Not known
General disorders and administration site		Common Uncommon	Not known Not known
conditions	Chest pain Oedema Oedema peripheral	Common	Not known
	Gravitational oedema Application site	Common Uncommon Common	
	oedema Mucosal dryness	Uncommon	
	Asthenia Fatigue	Common Very common	Not known
	Pyrexia Injection site reaction	Very common	Not known Not known
	Injection site inflammation Injection site mass	Common	Not known
	Injection site pain Injection site	Common	Not known Not known
	induration Injection site abscess sterile		Not known
	Injection site hematoma		Not known
	Chills Nodule		Not known Not known
	Thirst Malaise	Uncommon	Not known
	Influenza like illness Gait disturbance	Common Uncommon	Not known
Investigations	Inflammation Pelvic fibrosis Blood urea increased		Not known Not known Not known
Investigations	Blood urea increased Blood uric acid increased		Not known Not known
	Blood creatinine increased Bed blood cell		Not known
	Red blood cell sedimentation rate increased	Uncommon	
	Blood calcium increased Blood alkaline	Common	Not known
	phosphatase increased Blood lactic	Common	
	dehydrogenase increased		
	Prostatic Specific Antigen increased	Common	
	aminotransferase increased/ALT Aspartate	Common	
	aminotransferase increased/AST Gamma-	Common	
	glutamyltransferase increased		Netl
	Electrocardiogram abnormal ECG signs of	Common	Not known Not known
	myocardial ischemia Blood testosterone increased	Uncommon	
	Liver function test abnormal		Not known
	Platelet count decreased Blood potassium		Not known
	Blood potassium decreased White blood cell	Uncommon	Not known Not known
	count increased White blood cell count decreased		Not known
	Prothrombin time prolonged		Not known
	Activated partial thromboplastin time prolonged		Not known
	Cardiac murmur Low density		Not known Not known
	lipoprotein increased Blood triglycerides increased		Not known
	Increases		

Metabolism

In healthy male volunteers, a 1 mg bolus of leuprorelin acetate, 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 leuprorelin was metabolized into smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further metabolized.

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.

INDICATIONS

Prostate Cancer

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient

Endometriosis

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg 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

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is also 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

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is also indicated for the treatment of breast cancer in pre- and peri-menopausal women in whom hormone therapy is specified.

CONTRAINDICATIONS

- Leuprorelin Acetate for Depot Suspension 3 Month 11.25 mg is contraindicated in patients with known hypersensitivity to leuprorelin acetate, similar nonapeptides, or any of the excipients.
- Isolated cases of anaphylaxis have been reported with the monthly formulation of Leuprorelin Acetate for Depot Suspension.
- Leuprorelin Acetate for Depot Suspension 3 Month 11.25 mg is not suitable for the treatment of patients following an orchiectomy.
- Leuprorelin Acetate for Depot Suspension 3 Month 11.25 mg is contraindicated in patients with undiagnosed abnormal vaginal bleeding.
- Leuprorelin Acetate for Depot Suspension 3 Month 11.25 mg is contraindicated in women who are or may become pregnant while receiving the drug.

Leuprorelin acetate (Depot Formulation) once-a-month formulation, when administered one-time to rabbits on day six of pregnancy at test dosages of 0.00024, 0.0024 and 0.024 mg/kg (1/300 to 1/3 of the highest human dose), produced a dose-dependent increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprorelin acetate in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that fetal abnormalities and spontaneous abortion may occur if the drug is administered during pregnancy.

 Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg is contraindicated in women who are breastfeeding (see Lactation section

is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur. Prostate Cancer

See WARNINGS AND PRECAUTIONS, Men, Effect on QT/QTc Interval.

Drug/Laboratory Test Interactions

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

PRE-CLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats and mice. In rats, a doserelated increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprorelin acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg 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.

Mutagenicity studies have been performed with leuprorelin acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

It was not possible to perform a rat fertility study with the daily injection leuprorelin formulation. Based on leuprorelin pharmacological effects on pituitary-gonadal axis and based on findings in animals with leuprorelin depot formulations, leuprorelin may have adverse effects on male and female fertility.

Administration of leuprorelin acetate deopt formulation to male and female rate at doses of 0.024, 0.24, and 2.4 mg/kg monthly for 3 months (as low as 1/300 of the estimated monthly human dose) caused atrophy of the reproductive organs, and suppression of reproductive function.

Clinical and pharmacologic studies in females with leuprorelin acetate and similar analogues have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. There are no data in humans relating to male fertility following treatment with leuprorelin acetate.

Pregnancy

See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Women

Lactation

It is not known whether leuprorelin acetate is excreted in human milk. Therefore, it should not be used by nursing mothers.

ADVERSE REACTIONS

The following adverse reactions are commonly associated with the pharmacological actions of leuprorelin acetate on the steroidogenesis:

Men:

Neoplasm benign, malignant and unspecified (including cysts and polyps): prostate tumor flare, aggravation of prostate cancel

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

Skin and subcutaneous tissue disorders: dry skin, hyperhidrosis, rash, urticaria, hair growth abnormal, hair disorder, night sweats, hypotrichosis, pigmentation disorder, cold sweats, 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

Women

Metabolism and nutrition disorders: weight gain, weight loss

		Prostate Cancer 11.25 mg/3 month	Post-Marketing
System Organ Class	Preferred Term	Frequency	Frequency
Injury, poisoning	Fracture	Uncommon	
and procedural complications	Spinal fracture		Not known
	Head injury	Uncommon	
	Fall	Uncommon	
	Device occlusion	Uncommon	
Surgical and medical	Tumor excision	Uncommon	
procedures	Transurethral bladder resection	Uncommon	
	Lithotripsy	Uncommon	

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Ear and disorders Vertigo Common Menorrhagia Uncommon Menorrhagia Uncommon Motion sickness Common Auricular swelling Common			Uncommon	Uncommerci	Common	<u> </u>		Vulvovaginitis	Very common		Commo
Ear and Abyrinth disorders Vertigo Common Common Common Motion sickness Common Auricular swelling Common	ľ	Conjunctivitis		Uncommon	Common	Not known		Menorrhagia		Uncommon	<u> </u>
Deafness Common Motion sickness Common Auricular swelling Common		Drv eve		1	1	INCE NILOVVII		2	L		·
Motion sickness Common Auricular swelling Common	Ear and		Common								
	Ear and abyrinth	Vertigo	Common		Common						
There is a second sec	Ear and labyrinth disorders	Vertigo Deafness	Common								
Tinnitus Not known Hearing impaired Not known	Ear and labyrinth disorders	Vertigo Deafness Motion sickness Auricular swelling	Common		Common						

njury, poisoning	Class Preferred Terr		Jency mmon	Frequen	cy	Class	Preferred Term	Frequency	Frequency	Frequency	Frequency
and procedural complications	Spinal fracture Head injury	Unco	mmon	Not knov	vn	Cardiac disorders	Cardiac failure congestive Arrhythmia				Not known Not known
Surgical - '	Fall Device occlusio	n Unco	mmon mmon				Myocardial infarction Angina pectoris				Not known Not known
Surgical and mee procedures	Transurethral bl resection	adder Unco	mmon mmon				Tachycardia Palpitations Bradycardia	Uncommon Common	Uncommon	Common	Not known Not known
^a Depression and use of GnRH a	Lithotripsy d mood swing are con gonists.		mmon ved adverse r	eactions with	long-term	Vascular disorders	Hot flush Vasodilatation	Very	Very	Very common	
Nomen: Table 2 present	s ADRs and freque	ncies (verv	:ommon [>1	[/10]; comm	non [≥1/100		Lymphoedema	common	common		Not known
o <1/10]; unc requency base preast cancer o	ommon [≥1/1,000 ed upon available o :linical studies and) to <1/100 data]) from post-marke); not knov endometric eting experi	vn [ünable osis, uterine ence. A bla	to estimate fibroid and		Hypertension Phlebitis Thrombosis				Not known Not known Not known
hat the ADR v As leuprorelin a	was not seen from acetate has multiple e post-marketing	that partic	ular source , and theref	e. ore patient p	populations,		Hypotension Varicose vein				Not known Not known
every patient. elationship ha	For a majority of as not been establ	these adve ished.	erse reactio	ns, a cause	and effect	Respiratory, thoracic and mediastinal disorders	Pleural rub Pulmonary fibrosis	Uncommon		Common	Not known Not known
ncluding deep stroke, and tr	us venous and art vein thrombosis, ransient ischemic	pulmonary attack. Al	embolism, though a	myocardia temporal r	l infarction, elationship	alsorders	Epistaxis Dyspnoea Haemoptysis	Uncommon		Common Common	Not known Not known Not known
oncomitant r	in some cases, mo medication use. It use of GnRH agon	is unknow	n if there	is a causal	association		Dysphonia Sputum increased	Uncommon		Common	
Changes in B n controlled therapy) or ut	one Density clinical studies, p terine fibroids (th	atients wit	th endome	triosis (six	months of		Cough Pleural effusion Lung infiltration			Common	Not known Not known Not known
euprorelin der as measured b	bot 3.75 mg. In er by dual energy x-r 9% at six months	ndometriosi av absorpt	s patients, iometry (D	vertebral b EXA) decre	one density ased by an		Respiratory disorder Sinus congestion				Not known Not known
hose patients of therapy, me	who were tested an bone density re pot 3.75 mg was	at six or tw eturned to v	elve month vithin 2% c	s after disco of pretreatn	ontinuation nent. When		Pulmonary embolism Interstitial lung disease				Not known Not known
ibroid patien quantitative d	ts, vertebral trabe igital radiography baseline. Six moi	ecular bone (QDR) rev	e mineral c ealed a me	lensity as a ean decrea:	assessed by se of 2.7%	Gastrointestinal disorders		Common Very	Uncommon Common	Common Very	Not known Not known
	Table 2: Wc				apy, a tierra		Vomiting Nausea and vomiting	Common	Uncommon Uncommon	common Common	Not known
		Endo (11.25 mg)	Fibroids (11.25 mg)		Post- Marketing		Gastrointestinal haemorrhage				Not known
Class Infections and	Preferred Term	Frequency Uncommon	Frequency	Frequency	Frequency Not known		Abdominal distention Diarrhea	Uncommon Common	Common	Common Common	Not known Not known
infestations	Rhinitis Upper respiratory tract infection		Uncommon	Uncommon			Dysphagia Gingivitis			Common	Not known
	Pyelonephritis Furuncle	Uncommon Uncommon					Dyspepsia Flatulence Gastritis	Uncommon Uncommon Uncommon	Common	Common	
	Urinary tract infection Vulvovaginal		Uncommon		Not known		Gingival bleeding Dry mouth	Uncommon Common	Uncommon		Not known
	candidiasis Influenza		Uncommon		Net Jun		Abdominal pain Abdominal pain upper	Common	Common	Common	
	Pharyngitis Pneumonia Skin cancer				Not known Not known Not known		Abdominal pain lower			Common	
benign, malignant and unspecified (incl cysts and							Stomatitis Retching Duodenal ulcer			Common Common	Not known
polyps)	Leukopenia			Uncommon			Gastrointestinal disorder				Not known
system disorders	Anaemia Anaphylactic				Not known Not known	Hepato-biliary	Peptic ulcer Rectal polyp Liver tenderness	Uncommon			Not known Not known
disorder Endocrine disordors	reaction Goiter				Not known	disorders	Hepatic function abnormal			Common	Not known
Metabolism and nutrition	Pituitary apoplexy Anorexia Diabetes mellitus	Uncommon		Uncommon	Not known Not known		Serious liver injury Hepatic steatosis Jaundice			Common	Not known Not known
disorders .	Increased appetite	Uncommon	Uncommon	Very common	Not known	Skin and subcutaneous tissue disorders	Erythema Alopecia	Common		Common Common	Not known
	Decreased appetite Hypoglycaemia			Common	Not known		Ecchymosis Acne	Very common		Common	Not known
	Dehydration Hyperlipidaemia Hypercholesterolaemia	Common			Not known Not known		Seborrhea Rash	Common Common	Common	Common	Not known
	Hyperphosphataemia Hypoproteinaemia				Not known Not known		Rash maculo-papular Dry skin	Uncommon Common	Common		Not known
	Abnormal weight gain Abnormal loss of	Very common Common	Common Common	Very common Very			Photosensitivity reaction Urticaria	Uncommon			Not known Not known
	weight Affect lability	Very common	Common	common			Skin odour abnormal Hyperhidrosis	Common	Uncommon Common	Very common	
-	Mood swings ^a Personality disorder	Uncommon		Very common	Not known		Dermatitis Hair growth				Not known Not known
-	Nervousness	Very common	Common	Very common	Not known		abnormal Hirsutism Hair disorder	Common Uncommon	Uncommon		
	Libido decreased Libido increased	Very common	Common		Not known		Eczema Pruritus			Common	Not known
	Insomnia Sleep disorder	Very common	Common	Very common Common	Not known Not known		Nail disorder Skin discolouration		Uncommon Uncommon		
	Depression ^a	Very common	Common	Very common	Not known		Dermatitis bullous Pigmentation disorder		Uncommon		Not known
	Major depression Anxiety Delusion	Common Common Uncommon	Uncommon		Not known Not known	Musculoskeletal and connective	· · · · · · · · · · · · · · · · · · ·			Common	Not known
	Thinking abnormal Confusional state	Uncommon Common				tissue disorders		Uncommon	Uncommon Common		Not known Not known Not known
-	Euphoric mood Hostility	Uncommon Common					Arthralgia	Common	Common	Very common	Not known
	Apathy Nervousness/anxiety	Uncommon Very common					Back pain Osteoarthritis	Common	Common	Very common Common	
	Suicide ideation Suicide attempt Dizziness	Veni	Common	Venu	Not known Not known Not known		Arthritis Nuchal rigidity	Uncommon Common Common		Commer	
disorders	Dizziness postural	Very common		Very common Common			Neck pain Muscular weakness Musculoskeletal	common		Common Common Common	
·	Headache Paraesthesia	Very common Common	Very common Common	Very common Common	Not known Not known		stiffness Muscle twitching Ankylosing spondylitis			Common	Not known
	Lethargy Somnolence	Uncommon		Common	Not known	Renal and	Tenosynovitis Urinary incontinence	Uncommon			Not known Not known Not known
ŀ	Memory impairment Amnesia Dysgeusia	Uncommon	Uncommon	Common	Not known Not known	urinary disorders	Dysuria Pollakiuria	Common Uncommon		Common	Not known
	Hypoaesthesia Syncope	Uncommon		Common	Not known Not known		Micturition urgency Haematuria Bladder spasm				Not known Not known Not known
	Migraine Hypertonia	Common Common	Uncommon Common				Urinary tract disorder Urinary tract				Not known Not known Not known
r	Ataxia Tremor Neuropathy	Uncommon		Common	Not knows	Reproductive system and	obstruction Gynaecomastia				Not known
·	Neuropathy peripheral Cerebrovascular accident				Not known Not known	breast disorders	Breast tenderness Vaginal haemorrhage Menstrual disorder		Uncommon		Not known Not known Not known
	accident Loss of consciousness				Not known		Breast engorgement	Uncommon Uncommon			
	Transient ischemic attack Paralysis				Not known Not known		Breast atrophy Genital discharge	Common Common			
	Neuromyopathy Convulsion				Not known Not known		Vaginal discharge Galactorrhea Breast pain	Uncommon Common	Common	Common Common	Not known
Eye disorders	Vision blurred Eye disorder	Uncommon			Not known Not known		Pelvic pain Metrorrhagia	Common	Uncommon Uncommon		Not known Not known
,	Visual impairment Amblyopia	Common Common			Not known Not known		Menopausal symptoms Vulvovaginitis	Very	Very	Common	
ŀ		Uncommer		1		1	1 I I I I I I I I I I I I I I I I I I I	1.111		11 0 0	
	Eye pain Conjunctivitis Dry eye	Uncommon	Uncommon	Common	Not known		Menorrhagia	common	common Uncommon	Common	

		Endo (11.25 mg)	Fibroids (11.25 mg)	BC (11.25 mg)	Post- Marketin
System Organ Class	Preferred Term	Frequency	Frequency	Frequency	Frequenc
General	Pain	Common	Common		Not know
disorders and administration	Chest pain	Common	Uncommon	Common	
site conditions	Oedema	Common	Uncommon	Common	Not know
	Oedema peripheral	Common	Common	Common	
	Face oedema	Uncommon			
	Generalised oedema	Uncommon			
	Asthenia	Common	Common	Very common	Not know
	Fatigue			Common	Notknow
	Pyrexia Injection site reaction	Uncommon		Common Common	Not know Not know
	Injection site			Common	Not know
	inflammation				
	Injection site mass Injection site pain	Uncommon Common	Uncommon Common	Very	Not know
				common	
	Injection site induration			Very common	Not know
	Injection site pruritus			Common	
	Injection site erythema			Common	
	Injection site abscess sterile				Not know
	Injection site haematoma				Not know
	Chills	Common	Common		Not know
	Nodule				Not know
	Injection site hypersensitivity	Uncommon			
	Thirst	Common			Not know
	General physical health deterioration			Very common	
	Feeling hot			Very	
	l eening not			common	
	Irritability			Common	
	Malaise			Common	
	Condition		Uncommon		
	aggravated Inflammation				Not know
	Pelvic fibrosis				Not know
nvestigations	Blood urea increased				Not know
Incatigations	Blood uric acid increased				Not know
	Blood creatinine increased				Not know
	Blood calcium increased				Not know
	Body temperature increased			Uncommon	
	Occult blood positive			Common	
	Electrocardiogram abnormal				Not know
	ECG signs of myocardial ischemia				Not know
	Liver function test abnormal		Common		Not know
	Platelet count decreased				Not know
	Blood potassium decreased				Not know
	White blood cell count increased				Not know
	White blood cell count decreased				Not know
	Prothrombin time prolonged				Not know
	Activated partial thromboplastin time prolonged				Not know
	Laboratory test abnormal		Uncommon		
	Cardiac murmur				Not know Not know
	Low density lipoprotein increased				
	Blood triglycerides increased				Not know
nium	Blood bilirubin increased			Commi	Not know
njury, poisoning and procedural	Procedural pain Spinal fracture			Common	Not know

^a Depression and mood swing are commonly observed adverse reactions with long-term use of GnRH agonists.

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose of Leuprorelin Acetate Depot Suspension. In animal studies, doses of approximately 133 times the recommended human dose resulted in dyspnea, decreased activity and local irritation at the injection site. In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive supportive.

DOSAGE AND ADMINISTRATION

General

Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg must be administered under the supervision of a physician. Upon reconstitution, the suspension should be discarded if not used

immediately.

Reconstitute the microspheres immediately prior to administration, and administer as a single subcutaneous or intramuscular injection **every three months**.

- Preparation for Administration and Directions for Use
 For optimal performance of the Prefilled Dual chamber Syringe (PDS), read and follow the following instructions:
 1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
 Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
 Keen the syringe UPRIGHT. Gently mix the microspheres (particles) thoroughly
- Keep the syringe UPRIGHT. Gently mix the microspheres (particles) thoroughly to form a uniform suspension. The suspension will appear milky.
 Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
- 5. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
- 6. Inject the entire contents of the syringe intramuscularly or subcutaneously at the time of the reconstitution. The suspension settles very quickly following reconstitution; therefore, leuprorelin acetate should be mixed and used immediately.
- NOTE: Aspirated blood would be visible just below the luer lock if a blood vessel is accidentally penetrated. If present, blood can be seen in the needle hub.

STORAGE

The shelf life for this product is 36 months unopened. Do not store above 25°C. Once reconstituted with the sterile diluent, the suspension should be administered immediately. Protect from freezing.

HOW SUPPLIED

Leuprorelin Acetate PDS - 3 Month 11.25 mg is available in a single-dose administration kit of a syringe containing sterile lyophilized microspheres which are leuprorelin acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1 mL of diluent, Leuprorelin Acetate PDS -3 Month 11.25 mg is administered as a single subcutaneous or intramuscular injection. injection.

Manufacturer: AbbVie Logistics B.V., Meeuwenlaan 4, 8011 BZ Zwolle, The Netherlands

License Holder: AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved.

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