SUMMARY OF PRODUCT CHARACTERISTICS

LECTRUM ® 3.75 mg Injection
(Leuprolide acetate)

1. Name of the medicinal product

1.1 Strength

Lectrum ® 3.75 mg

1.2 Pharmaceutical form

Lyophilized powder for suspension for injection
1 vial with lyophilized microspheres+ 1 solvent ampoule for intramuscular/ subcutaneous use.

2. Qualitative and quantitative composition

Lectrum 3.75 mg Each vial contains: Leuprolide acetate ……..3.75mg	
Leuprolide acetate	3.75 mg
Gelatin	0.65 mg
PLGA*	33.10 mg
Mannitol	6.60 mg

* PLGA: co-polymer of DL-lactic/glycolic acid (75:25 mol %)

3. PHARMACEUTICAL FORM

4. Clinical particulars

4.1 Therapeutic indications

Lectrum ® 3.75 mg is indicated:

- In metastatic prostate cancer.
- In locally advanced prostate cancer, as an alternative to surgical castration.
- As an adjuvant treatment to radiotherapy in patients with high-risk localized or locally advanced prostate cancer.
- As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.
- Uterine Fibroids Lectrum ® 3.75 mg is indicated in the treatment of leiomyoma uteri (uterine fibroids) for a period of six months. Therapy may be preoperative prior to myomectomy or hysterectomy or it may provide symptomatic relief for the premenopausal woman who does not desire surgery.

Endometriosis Lectrum ® 3.75 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.
Central Precocious Puberty Lectrum ® 3.75 mg is indicated in the treatment of children with central precocious puberty (CPP). Children should be selected using the following criteria:
1. Clinical diagnosis of CPP (idiopathic or neurogenic) with onset of secondary sexual characteristics earlier than eight years in females and nine years in males.
2. Clinical diagnosis should be confirmed prior to initiation of therapy: - Confirmation of diagnosis of a pubertal response to a gonadotropin releasing hormone (GnRH) stimulation test. The sensitivity and methodology of this assay must be understood. - Bone age advanced one year beyond the chronological age.

3. Baseline evaluation should also include: - Height and weight measurements - Sex steroid levels - Adrenal steroid level to exclude congenital adrenal hyperplasia - Beta human chorionic gonadotropin level to rule out a chorionic gonadotropin secreting tumor - Pelvic/adrenal/testicular ultrasound to rule out a steroid secreting tumor - Computerized tomography of the head to rule out intracranial tumor. Breast Cancer Lectrum ® 3.75 mg is indicated for the treatment of breast cancer in pre- and premenopausal women in which hormone therapy is specified.

4.2 Posology and method of administration

Lectrum ® 3.75 mg must be administered under the supervision of a physician.
As with other medicines administered by injection, the injection sites should be varied periodically.
For instructions on the reconstitution of the medicine before administration, see section 6.6.
Prostate Cancer
The recommended dose of Lectrum ® 3.75 mg is one injection given intramuscularly or subcutaneously every month.

Generally, the treatment of advanced, hormone-sensitive prostate cancer is continued on a long-term basis. In view of potential clinical signs of progression presenting despite adequate treatment, treatment with Lectrum ® 3.75 mg should be monitored for success on a regular basis by means of clinical examinations as well as laboratory evaluations of prostate-specific antigen (PSA), and serum testosterone levels. As animal experimental findings demonstrated, it is crucial to avoid accidental intra-arterial injection, in view of the potential onset of thrombosis of small vessels distal to the injection site. In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of castration-resistant prostate cancer.

Uterine Fibroids, Endometriosis and Breast Cancer

- The recommended dose of Lectrum ® 3.75 mg is one injection given intramuscularly or subcutaneously every month.
- The recommended dose of Lectrum ® 3.75 mg is one injection given intramuscularly or subcutaneously every three months.
- Use of Lectrum ® 3.75 mg in treatment of benign gynaecological conditions should be limited to six months because of possible osteoporotic effects

Posology

Initial Dose The recommended starting dose of Lectrum ® 3.75 mg is 0.3 mg/kg (minimum 7.5 mg), administered either intramuscularly or subcutaneously.

The starting dose is dictated by the child's weight, as follows:

Child's Weight (kg)	**Actual Dosage**	**Number of Injection Sites**	**Total Dosage**
<25kg	3.75mg x 2	1	7.5mg
>25 to 37.5kg	3.75mg x 3	2	11.25mg
>37.5kg	3.75mg x 4	3	15mg

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

Maintenance Dose

If total down-regulation 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.

Information for Parents of Children Treated with Lectrum ® 3.75 mg for Central Precocious Puberty

Prior to starting therapy with Lectrum ® 3.75 mg, the parent or guardian must be aware of the importance of continuous therapy. Adherence to four week medicine administration schedules must be accepted if therapy is to be successful.

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

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

- Report any unusual signs or symptoms to the physician.

4.3 Contraindications

Lectrum ® 3.75 mg is contraindicated in patients with known hypersensitivity to leuprorelin acetate or similar nonpeptides or to any of the excipients listed in section 6.1.

Isolated cases of anaphylaxis have been reported.

In case hormone-independence of the carcinoma has been demonstrated, treatment with Lectrum ® 3.75 mg PDS Injection is not indicated.

After surgical castration, Lectrum ® 3.75 mg PDS Injection does not offer further reduction of testosterone levels.

Lectrum ® 3.75 mg is contraindicated in women who are or may become pregnant while receiving treatment with this medicine (see sections 4.6 and 5.3).

Lectrum ® 3.75 mg is also contraindicated in women during breastfeeding.

Lectrum ® 3.75 mg should not be administered to patients with undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

General

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the medicine. Therefore, an increase in clinical signs and symptoms may be observed (see section 5.1).

Isolated cases of worsening of pre-existing signs and symptoms during the first weeks of treatment have been reported with LH-RH analogues. Worsening of symptoms may contribute to paralysis with or without fatal complications.

Bone Mineral Density

Bone mineral density changes can occur during any hypo-oestrogenic state in women and in long-term use in prostate cancer in men. There are no data regarding reversibility after withdrawal of leuprorelin acetate. In women, bone mineral density loss may be reversible after withdrawal of leuprorelin acetate.

Convulsions

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

Delayed Hypersensitivity Reactions

Delayed hypersensitivity reactions including the severe cutaneous adverse reactions (SCAR) of Stevens- Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been very rarely reported postmarketing in association with leuprorelin acetate therapy (see Section 4.8 Undesirable Effects - Clinical and Postmarketing). Discontinue future leuprorelin acetate therapy at first signs or symptoms of a delayed hypersensitivity reaction, and treat patients according to current clinical practice.

Men

Prostate cancer

Flare Effect

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. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

Metabolic changes

The use of androgen deprivation therapy, including GnRH agonists, may be associated with an increased risk of metabolic changes such as hyperglycaemia, diabetes, hyperlipidaemia, and non-alcoholic fatty liver disease (NAFLD). Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Patients at increased risk should be monitored for the signs and symptoms of metabolic syndrome including lipids, blood glucose and/or glycosylated haemoglobin (HbA1C), and managed according to current clinical practice (see Section 4.8 Undesirable Effects).

Cardiovascular disease

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 to be 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 practice.

Effect on QT/QTc Interval

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

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

Effect on Laboratory Tests – Prostate Cancer

Response to leuprorelin acetate should be monitored by measuring serum levels of testosterone, as well as prostate specific antigen 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 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. Transient increases in acid phosphatase levels sometimes occur early in treatment. However, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline.

Women

Since loss of bone density can be anticipated as part of the natural menopause, it may also be expected to occur during a medically induced hypo-oestrogenic state. Bone loss has been found to be reversible after completion of a six month course of leuprorelin acetate.

Repeat courses of leuprorelin acetate or any other GnRH agonist following an initial six month course of therapy should not be considered without assessment of the risk of developing osteoporosis. No data are available for women receiving the treatment for a longer period of time.

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 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.

Paediatric Population

Central Precocious Puberty

Non-compliance with medicine 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.

Bone Mineral Density – Central Precocious Puberty

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.

Pseudo tumor cerebri/idiopathic intracranial hypertension

Pseudo tumor cerebri (PTC) / idiopathic intracranial hypertension has been reported in Paediatric patients receiving leuprorelin acetate. Monitor patients for signs and symptoms of PTC, including headache, papilloedema, and blurred vision, and 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 papilloedema. If PTC is confirmed, treat the patient in accordance with the established treatment guidelines and permanently discontinue use of leuprorelin acetate.

Effect on Laboratory Tests – Central Precocious Puberty

Response to leuprorelin acetate 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.

Sex steroids may increase or rise above pre-pubertal levels if the dose is inadequate. Once a therapeutic dose has been established, gonadotropin and sex steroid levels will decline to pre-pubertal levels.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic-based medicine-medicine interaction studies have been conducted with leuprorelin acetate depot suspension. However, because leuprorelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the medicine is only about 46% bound to plasma proteins, medicine interactions would not be expected to occur.

Prostate Cancer

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

Laboratory Test Interactions

Administration of Lectrum ® 3.75 mg in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of Lectrum ® 3.75 mg may be misleading.

4.6 Fertility, pregnancy and lactation

Fertility

Clinical and pharmacological studies with leuprorelin acetate and similar analogues have shown full reversibility of fertility suppression when the therapy is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy (Category D)

The safe use of leuprorelin acetate in pregnancy has not been established clinically. Studies in animals have shown reproductive toxicity (see section 5.3). Before starting treatment with leuprorelin acetate, it is advisable to establish whether the patient is pregnant. Leuprorelin is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used (see section 4.3).

Lactation

It is not known whether leuprorelin acetate is excreted in human milk; therefore, Lectrum ® 3.75 mg should not be used by nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

There are no reported effects on the ability to drive or operate machinery. However, as with all medicines, care should be taken until the individual effects of Lectrum ® 3.75 mg are known.

4.8 Undesirable effects

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 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 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
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, 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.

Children:
Psychiatric disorders: affect lability Nervous system disorders: headache
Vascular disorders: vasodilatation
Skin and subcutaneous tissue disorders: acne/seborrhea, 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

Clinical and Post marketing

The following sections present adverse reactions seen in clinical studies or postmarketing experience. They are arranged by patient population: Men, Women, and Children.
Men:

Prostate Cancer

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 (5)].**

Response to Lectrum ® 3.75 mg can be verified by monitoring serum testosterone, acid phosphatase, and PSA (prostate-specific antigen) levels. Specifically, there occurs an initial temporary rise in the testosterone level at the start of treatment, followed by a decrease within a period of two weeks. After two to four weeks testosterone levels are reached similar to those observed after bilateral orchiectomy and persisting in the castration range throughout the entire treatment period.

In the initial phase of therapy with Lectrum ® 3.75 mg, a transient rise in acid phosphatase may occur. However, acid phosphatase values usually return to normal or near-normal within a few weeks.

The resulting hypogonadism, commonly observed under long-term therapy with GnRH analogues or orchiectomy, may lead to the onset of osteoporosis, with the increased risk for bone fracture (see section 4.4). In patients at risk, the additional administration of a bisphosphonate may prevent such bone demineralization.

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). A blank indicates that the ADR was not seen from that particular source.

Table 1: Prostate Cancer			
System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
Infections and infestations	Rhinitis	Uncommon	
	Bronchitis		Common
	Urinary tract infection		Common
	Infected cyst		Uncommon
	Viral infection		Uncommon
	Candidiasis		Uncommon
	Sepsis		Uncommon
	Fungal skin infection	Uncommon	

Table 1: Prostate Cancer			
System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**

		Frequency	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm	Uncommon	
	Pseudo-lymphoma		Uncommon
Blood and lymphatic system disorder	Anaemia		Common
	Eosinophilia		Uncommon
Immune system disorders	Hypersensitivity		Uncommon
Metabolism and nutrition disorders	Anorexia	Common	Common
	Hyperglycaemia	Uncommon	Uncommon
	Hypoglycaemia		Uncommon
	Dehydration		Uncommon
	Abnormal weight gain	Uncommon	Very common
	Abnormal loss of weight		Common
Psychiatric disorders	Libido decreased	Common	Very common
	Insomnia	Uncommon	Common
	Sleep disorder	Uncommon	
	Depression[a]	Uncommon	Common
Nervous system disorders	Dizziness	Uncommon	Uncommon
	Headache		Common
	Paraesthesia	Uncommon	Common
	Somnolence	Uncommon	Uncommon
	Tremor		Uncommon
	Simple partial seizures		Uncommon
Eye disorders	Amblyopia	Uncommon	
Ear and labyrinth disorders	Ear pain	Uncommon	
	Tinnitus	Uncommon	
Cardiac disorders	Arrhythmia	Uncommon	

Table 1: Prostate Cancer

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**

		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
	Angina pectoris	Uncommon	Uncommon
	Ventricular extrasystoles	Uncommon	
	Cardiac failure		Uncommon
	Bradycardia		Uncommon
	Atrioventricular block		Uncommon
Vascular disorders	Hot flush	Very common	Very common
	Vasodilatation	Very common	
	Angiopathy	Uncommon	
	Lymphoedema		Common
	Hypertension	Uncommon	Common
	Thrombophlebitis		Common
	Aneurysm		Uncommon
	Circulatory collapse		Uncommon
	Flushing		Uncommon
	Haematoma		Uncommon
	Poor peripheral circulation	Uncommon	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon	
	Dyspnoea	Common	Common
	Haemoptysis	Uncommon	
	Emphysema	Uncommon	
	Cough		Uncommon
	Asthma		Common
	Chronic obstructive pulmonary disease		Uncommon
Gastro-intestinal disorders	Constipation		Common

	Nausea	Common	Common
Table 1: Prostate Cancer			
System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
	Vomiting	Common	
	Gastritis		Uncommon
	Diarrhoea	Common	
Hepato-biliary disorder	Hepatitis cholestatic		Uncommon
	Hepatocellular injury		Uncommon
Skin and subcutaneous tissue disorders	Alopecia	Uncommon	Uncommon
	Rash	Uncommon	Uncommon
	Rash maculo-papular	Uncommon	
	Dry skin		Uncommon
	Hyperhidrosis	Common	Very common
	Hair disorder	Uncommon	
	Pruritus	Common	Common
	Night sweats	Uncommon	
Musculo-skeletal and connective tissue disorders	Bone pain	Uncommon	Very common
	Myalgia	Uncommon	Uncommon
	Arthralgia	Common	Common
	Back pain		Common
	Muscular weakness	Uncommon	Common
	Pain in extremity	Uncommon	Common
	Muscle spasms		Uncommon
Renal and urinary disorders	Urinary incontinence		Uncommon
	Dysuria	Uncommon	Common

	Pollakiuria	Uncommon	Uncommon
	Haematuria	Uncommon	Common
	Nocturia		Very common
	Urinary retention	Uncommon	Uncommon

Table 1: Prostate Cancer

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
	Micturition disorder		Uncommon
	Polyuria	Uncommon	
Reproductive system and breast disorders	Gynaecomastia	Uncommon	Common
	Erectile dysfunction	Common	Very common
	Testicular atrophy	Common	
	Breast enlargement	Uncommon	
	Testicular disorder		Very common
General disorders and administration site conditions	Pain	Common	Common
	Chest pain	Uncommon	Uncommon
	Oedema peripheral	Common	Common
	Gravitational oedema		Uncommon
	Application site oedema		Common
	Mucosal dryness		Uncommon
	Asthenia	Uncommon	Common
	Fatigue	Common	Very common
	Injection site reaction		Very common
	Injection site inflammation	Uncommon	
	Injection site mass		Common
	Injection site pain	Common	Common

	Injection site induration	Common	
	Injection site erythema	Uncommon	
	Injection site irritation	Uncommon	
	Chills	Uncommon	
	Malaise		Uncommon
	Influenza like illness		Common
	Gait disturbance		Uncommon

Table 1: Prostate Cancer

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
Investigations	Haemoglobin decreased	Uncommon	
	Blood urea increased	Uncommon	
	Blood uric acid increased	Uncommon	
	Red blood cell sedimentation rate increased		Uncommon
	Blood calcium increased	Uncommon	
	Blood alkaline phosphatase increased	Common	Common
	Blood lactic dehydrogenase increased	Very common	Common
	Prostatic Specific Antigen increased		Common
	Alanine aminotransferase increased/(ALT)	Uncommon	Common
	Aspartate aminotransferase increased/(AST)	Common	Common
	Gammaglutamyl-transferase increased	Uncommon	Common

	Electrocardiogram abnormal		Common
	Blood testosterone increased		Uncommon
	Platelet count decreased	Uncommon	
	Protein urine present	Uncommon	
	White blood cell count increased	Uncommon	
	Reticulocyte count increased	Uncommon	
Injury, poisoning and procedural complications	Fracture		Uncommon
	Head injury		Uncommon

Table 1: Prostate Cancer

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**	
		3.75 mg, 7.5 mg/ 1 month (M85-097,TAP-144-SR-2/ PD-115-PC, M85-101, n = 230)	**11.25 mg/ 3 month (EC001, EC002, n = 181)**
		Frequency	
	Fall		Uncommon
	Device occlusion		Uncommon
Surgical and medical procedures	Tumor excision		Uncommon
	Transurethral bladder resection		Uncommon
	Lithotripsy		Uncommon

Women:

Table 2 presents ADRs and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). A blank indicates that the ADR was not seen from that particular source.
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.

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 leuprorelin depot 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% 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 pretreatment. When leuprorelin depot

3.75 mg 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: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
Infections and infestations	Infection	Uncommon				Uncommon
	Rhinitis		Uncommon			Uncommon
	Upper respiratory tract infection			Uncommon	Uncommon	
	Pyelonephritis	Uncommon				
	Furuncle	Uncommon				
	Urinary tract infection			Common		Common
	Vulvovaginal candidiasis		Uncommon			Common
	Influenza		Uncommon			Common
	Pharyngitis					Common
	Nasopharyngitis			Common		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasm					Uncommon
Blood and	Leukopenia			Uncommon	Uncommon	

lymphatic	Iron deficiency anaemia			Common		

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
system disorder	Lymph-adenopathy					Uncommon
	Coagulopathy					Uncommon
Endocrine disorders	Thyroiditis					Common
Metabolism and nutrition disorders	Anorexia	Uncommon		Uncommon	Uncommon	
	Increased appetite	Uncommon	Uncommon	Very common	Very common	Common
	Decreased appetite			Common	Common	
	Hypercholesterolaemia	Common				
	Abnormal weight gain	Very common	Common	Very common	Very common	Very common
	Abnormal loss of weight	Common	Common	Very common	Very common	Common
Psychiatric disorders	Affect lability	Very common	Common	Common		Very common
	Mood swings[a]			Very common	Very common	
	Personality disorder	Uncommon				

	Nervousness	Very common	Common	Very common	Very common	Very common

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Libido decreased	Very common	Common			Common
	Insomnia	Very common	Common	Very common	Very common	Very common
	Sleep disorder			Common	Common	
	Depression[a]	Very common	Common	Very common	Very common	Very common
	Major depression	Common				
	Anxiety	Common	Uncommon	Common		Common
	Delusion	Uncommon				
	Thinking abnormal	Uncommon				Common
	Confusional state	Common				Uncommon
	Euphoric mood	Uncommon				
	Hostility	Common				Uncommon
	Apathy	Uncommon				
	Agitation					Common
	Nervousness/ anxiety	Very common				

	Screaming					Uncommon
	Dizziness	Very common	Common	Very common	Very common	Common

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Dizziness postural			Common	Common	
	Headache	Very common	Very common	Very common	Very common	Very common
	Paraesthesia	Common	Common	Common	Common	Common
	Somnolence	Uncommon		Common	Common	Common
	Memory impairment				Common	
	Amnesia	Uncommon				Common
	Dysgeusia		Uncommon			Uncommon
Nervous system disorders	Hypoaesthesia				Common	Common
	Syncope	Uncommon				Common
	Migraine	Common	Uncommon			Very common
	Hypertonia	Common	Common			Common
	Ataxia	Uncommon				
	Tremor			Common	Common	Common
	Coordination abnormal					Common
	Hyperkinesia					Common

	Convulsions local			Common		
Eye disorders	Vision blurred			Common		
	Eye disorder	Uncommon				

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Visual impairment	Common				
	Amblyopia	Common				Common
	Eye pain	Uncommon				
	Conjunctivitis		Uncommon	Common	Common	
Ear and labyrinth disorders	Ear pain					Uncommon
	Vertigo	Common				
	Deafness				Common	
	Motion sickness				Common	
	Auricular swelling				Common	
	Tinnitus			Common		
Cardiac disorders	Tachycardia	Uncommon	Uncommon			Common
	Palpitations	Common		Common	Common	Common
Vascular disorders	Hot flush			Very common	Very common	
	Vasodilatation	Very common	Very common			Very common
	Hypertension					Common

Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon		Common	Common	
	Dyspnoea			Common	Common	
	Dysphonia	Uncommon				Uncommon

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Sputum increased				Common	
	Cough			Common	Common	
	Laryngospasm					Uncommon
	Oropharyngeal pain			Common		
Gastro-intestinal disorders	Constipation	Common	Uncommon	Common	Common	Common
	Nausea	Very common	Common	Very common	Very common	Very common
	Vomiting		Uncommon	Common	Common	Common
	Nausea and vomiting	Common	Uncommon			Common
	Abdominal distention	Uncommon			Common	Common
	Diarrhoea	Common	Common	Common	Common	Common
	Gingivitis				Common	Common
	Dyspepsia	Uncommon				Common
	Flatulence	Uncommon	Common			Common

	Gastritis	Uncommon			Common	
	Gingival bleeding	Uncommon				
	Dry mouth	Common	Uncommon			Uncommon
	Abdominal pain	Common	Common	Common		Common

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Abdominal pain upper			Common	Common	
	Abdominal pain lower			Common	Common	
	Stomatitis			Common	Common	
	Retching			Common	Common	
	Melaena					Common
	Colitis					Uncommon
	Abdominal discomfort			Common		
	Tongue disorder			Common		
Hepatobiliary disorder	Liver tenderness	Uncommon				
	Hepatic function abnormal				Common	
	Hepatic steatosis				Common	
Skin and	Erythema			Common	Common	

subcutaneous tissue disorders	Alopecia	Common		Common	Common	Common
	Ecchymosis	Common				Common
	Acne	Very common		Common	Common	Very common
	Seborrhoea	Common				
	Rash	Common	Common		Common	Common

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Rash maculo-papular	Uncommon				
	Dry skin	Common	Common			Common
	Photosensitivity reaction	Uncommon				
	Urticaria			Common		Uncommon
	Skin odour abnormal		Uncommon			
	Hyperhidrosis	Common	Common	Very common	Very common	Very common
	Dermatitis bullous		Uncommon			
	Hirsutism	Common	Uncommon			Uncommon
	Hair disorder	Uncommon				Common
	Eczema				Common	
	Pruritus					Common
	Nail disorder		Uncommon			Common

	Skin discolouration		Uncommon			Uncommon
	Skin disorder					Uncommon
	Skin nodule					Common
	Night sweats			Common		
	Pigmentation disorder			Common		

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
Musculo-skeletal and connective tissue disorders	Bone pain			Common	Common	
	Myalgia	Uncommon	Uncommon			Common
	Arthropathy	Common	Common			Common
	Arthralgia	Common	Common	Very common	Very common	Common
	Back pain	Common	Common	Very common	Very common	Common
	Osteoarthritis				Common	
	Arthritis	Uncommon				
	Nuchal rigidity	Common				Uncommon
	Neck pain	Common		Common	Common	Uncommon
	Muscular weakness			Common	Common	
	Musculoskeletal stiffness			Common	Common	

	Muscle twitching				Common	Uncommon
	Muscle spasms					Common
	Periarthritis			Common		
Renal and urinary disorders	Urinary incontinence	Uncommon				
	Dysuria	Common				Uncommon
	Pollakiuria	Uncommon		Common	Common	
	Nocturia			Common		

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Renal pain					Common
Reproductive system and breast disorders	Vaginal haemorrhage					Uncommon
	Dysmenorrhea			Common		Common
	Menstrual disorder		Uncommon			
	Breast enlargement	Uncommon				Common
	Breast engorgement	Uncommon				
	Breast atrophy	Common				Common
	Genital discharge	Common				

	Vaginal discharge				Common	
	Galactorrhoea	Uncommon				Common
	Breast pain	Common	Common		Common	Very common
	Pelvic pain	Common	Uncommon			Common
	Metrorrhagia		Uncommon	Common	Common	Uncommon
	Menopausal symptoms			Common	Common	
	Dyspareunia					Common
	Uterine disorder					Uncommon

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Vulvovaginitis	Very common	Very common	Common	Common	Very common
	Menorrhagia		Uncommon	Common		
General disorders and administration site conditions	Pain	Common	Common			Very common
	Chest pain	Common	Uncommon	Common	Common	Common
	Oedema	Common	Uncommon	Common	Common	
	Oedema peripheral	Common	Common	Common	Common	Common
	Face oedema	Uncommon				
	Generalised oedema	Uncommon				Common

	Asthenia	Common	Common	Very common	Very common	Very common
	Fatigue			Common	Common	
	Pyrexia			Common	Common	Common
	Injection site reaction	Uncommon		Common	Common	Common
	Injection site mass	Uncommon	Uncommon			
	Injection site pain	Common	Common	Very common	Very common	Common
	Injection site induration			Very common	Very common	

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Injection site pruritus			Common	Common	
	Injection site erythema			Common	Common	
	Injection site haemorrhage			Common		
	Chills	Common	Common			Common
	Injection site hypersensitivity	Uncommon				
	Thirst	Common				

	General physical health deterioration			Very common	Very common	
	Feeling hot			Very common	Very common	
	Irritability			Common	Common	
	Malaise			Common	Common	Common
	Condition aggravated		Uncommon			
Investigations	Body temperature increased			Uncommon	Uncommon	
	Occult blood positive				Common	

Table 2: Women Indications

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**				
		Endometriosis (3.75 mg, 11.25 mg: M86-031, M86-039, n = 166)	**Uterine fibroids (3.75 mg, 11.25 mg: M86-034, M86-049, M86-062, M90-411, n = 167)**	**Breast cancer (3.75 mg: CPH-101, B02/EC 008, n = 365)**	**Breast cancer (11.25 mg: CPH-101, B02/EC 008, n = 365)**	**Add-back (3.75 mg, 11.25 mg: M92-878, M97-777, n = 191)**
		Frequency				
	Liver function test abnormal		Common			
	Laboratory test abnormal		Uncommon			
Injury, poisoning and procedural complications	Procedural pain				Common	

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

Children:
Table 3 presents ADRs and frequencies (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). A blank indicates that the ADR was not seen from that particular source.
Psychiatric Events
Psychiatric events have been reported in patients taking GnRH agonists. Postmarketing reports with this class of drugs 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. Monitor for development or worsening of psychiatric symptoms during treatment with leuprorelin acetate.

Table 3: Central Precocious Puberty

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**
		CPP 1 Month (3.75, 7.5, 11.25, 15 mg: P90-053, M90-516, n=421)
		Frequency
Infections and infestations	Infection	Uncommon
	Rhinitis	Uncommon
	Influenza	Uncommon
	Pharyngitis	Uncommon
	Sinusitis	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Cervix neoplasm	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
Endocrine disorders	Precocious puberty	Uncommon
	Goitre	Uncommon
Metabolism and nutrition disorders	Growth retardation	Common
	Abnormal weight gain	Common
	Increased appetite	Uncommon
Psychiatric disorders	Affect lability	Common
	Nervousness	Uncommon
	Depression[a]	Uncommon
Nervous system disorders	Headache	Common
	Somnolence	Uncommon
	Syncope	Uncommon
	Hyperkinesia	Uncommon

Cardiac disorders	Bradycardia	Uncommon
Vascular disorders	Vasodilatation	Common
	Hypertension	Uncommon
	Peripheral vascular disorder	Uncommon
	Epistaxis	Uncommon

Table 3: Central Precocious Puberty

	Preferred Term	**Dose/Formulation (clinical study)**
System Organ Class		**CPP 1 Month (3.75, 7.5, 11.25, 15 mg: P90-053, M90-516, n=421)**
		Frequency
Respiratory, thoracic and mediastinal disorders	Asthma	Uncommon
Gastrointestinal disorders	Constipation	Uncommon
	Nausea and vomiting	Uncommon
	Dysphagia	Uncommon
	Gingivitis	Uncommon
	Dyspepsia	Uncommon
Skin and subcutaneous tissue disorders	Alopecia	Uncommon
	Acne	Common
	Rash	Common
	Skin odour abnormal	Common
	Hirsutism	Uncommon
	Hair disorder	Uncommon
	Nail disorder	Uncommon
	Leukoderma	Uncommon
	Skin hypertrophy	Uncommon
	Purpura	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Uncommon
	Arthropathy	Uncommon
	Myopathy	Uncommon

	Arthralgia	Uncommon
Renal and urinary disorders	Urinary incontinence	Uncommon
Reproductive system and breast disorders	Gynaecomastia	Common
	Vulvovaginitis	Common
	Vaginal haemorrhage	Uncommon
	Cervix disorder	Uncommon

Table 3: Central Precocious Puberty

System Organ Class	**Preferred Term**	**Dose/Formulation (clinical study)**
		CPP 1 Month (3.75, 7.5, 11.25, 15 mg: P90-053, M90-516, n=421)
		Frequency
	Dysmenorrhea	Uncommon
	Menstrual disorder	Uncommon
	Breast enlargement	Uncommon
	Vaginal discharge	Uncommon
	Breast pain	Uncommon
	Feminisation acquired	Uncommon
General disorders and administration site conditions	Pain	Common
	Oedema peripheral	Uncommon
	Pyrexia	Uncommon
	Injection site reaction	Common
	Hypertrophy	Uncommon
	Condition aggravated	Uncommon
Investigations	Antinuclear antibody positive	Uncommon
	Red blood cell sedimentation rate increased	Uncommon
Depression and mood swings are commonly observed adverse reactions with long term use of GnRH agonists.		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after a drug has been authorized is important. It enables ongoing monitoring of the drug's risk/benefit ratio. Healthcare professionals report all suspected adverse reactions via the national reporting system:

http://agp.com.pk/adverse-event-form/
You can also report side effects to DRAP through MED Vigilance E-Reporting system of DRAP available online at: https://primaryreporting.who-umc.org/pk

4.9 Overdose

There is no clinical experience with the effects of an acute overdose of Lectrum ® 3.75 mg. In animal studies, doses of approximately 133 times the recommended human dose of leuprorelin acetate resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of over dosage, the patients should be monitored closely and management should be symptomatic and supportive.

5.1 Pharmacodynamics properties

5.1.1 Pharmacotherapeutic group

Gonadotrophin-Releasing Hormone Analogues

ATC code: L02AE 02.

5.1.2 Mechanism of action

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 causes inhibition of the growth of certain hormone dependent tumours (prostatic tumours in Nobel and Dunning male rats and DMBA-induced mammary tumours 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 luteinising hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and oestrone and oestradiol 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 prepubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating medicine therapy at recommended doses.

Prostate Cancer

The growth and function of the prostate gland is dependent upon the male hormone, testosterone. Treatment of prostatic carcinoma is aimed at achieving a testosterone blockage (chemical castration). Continuous administration of leuprorelin acetate in males results in a decrease of testosterone to castrate or prepubertal levels. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

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.

Uterine Fibroids and Endometriosis

Since oestrogen stimulates the growth of both uterine and endometrial tissue, the treatment of uterine fibroids and endometriosis with leuprorelin acetate is based on suppression of oestrogen production.

Uterine Fibroids

Leiomyoma uteri (uterine fibroids) is a gynaecological disorder characterised by the presence of benign tumours of myometrial origin, for which oestrogen usually functions as a growth-promoting factor. The effect of oestrogen depletion on the leiomyoma results in shrinkage of the fibroids and in alleviation of the symptoms, including menorrhagia and pelvic pain, pressure and discomfort. Improvement in haemoglobin and haematocrit has been noted following reduction or elimination of menorrhagia.

Endometriosis

The aetiology of endometriosis is unclear, but several theories exist regarding its origin. The most probable cause is retrograde menstruation, but other possible sources included surgical transplantation and direct extension of the endometrium. Medical therapy in endometriosis is based on suppression of oestrogen production. The hypo-oestrogenic state resulting from the administration of Lectrum ® 3.75 mg produced atrophic changes in both uterine and ectopic endometrial tissue. This process included abatement of current endometrial implants, prohibition of new lesions, and possible reduction of adhesions, all of which can result in decreased pain and symptoms. In clinical trials, the majority of women experienced improvement in one or more of the signs and symptoms of endometriosis.

Suppression of pituitary gonadotropins usually results in elimination of the menstrual cycle. In conjunction with a 6 month course of therapy, following the last 28 day therapeutic period, the median time to resumption of menses was 52 days (range 7 to 183) in the uterine fibroids clinical studies and 51 days (range 9 to 142) in the endometriosis studies.

Since both oestrogen and androgen steroidogenesis are suppressed, the androgenic effects seen with other therapies are avoided.

Central Precocious Puberty

Central Precocious Puberty (CPP) is a rare condition defined as the appearance of any signs of secondary sexual development before the age of 8 in females and 9 in males. CPP is caused by the premature activation of the hypothalamic-pituitary-gonadal axis in the same pattern as occurs at puberty.

In children with CPP, stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and oestradiol are reduced to prepubertal levels in males and females, respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprorelin acetate.

The following physiologic effects have been noted with the chronic administration of leuprorelin 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 pre-pubertal state.

3. **Menses**. Menses, if present, will cease.

In a study of 22 children with CPP, doses of leuprorelin acetate for depot suspension were given every four weeks and plasma levels were determined according to weight categories as summarized in the following table:

Patient Weight Range (kg)	**Group Weight Average (kg)**	**Dose (mg)**	**Trough Plasma Leuprorelin Level Mean ± SD (ng/mL)***
20.2 to 27.0	22.7	7.5	0.77 ± 0.33
28.4 to 36.8	32.5	11.25	1.25 ± 0.06

39.3 to 57.5	44.2	15	1.59 ± 0.65
*Group average values determined at Week 4 immediately prior to leuprorelin acetate injection. Drug levels at 12 and 24 weeks were similar to respective 4 week levels.			

5.2 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
Leuprorelin Acetate for Depot Suspension 3.75 mg Paediatric

Following the administration of a 7.5 mg of leuprorelin acetate for depot suspension injection to adult patients, mean peak leuprorelin plasma concentration was almost 20 ng/mL at four hours and then declined to 0.36 ng/mL at four weeks. However, intact leuprorelin and an inactive major metabolite could not be distinguished by the assay which was employed in the study.

Non-detectable leuprorelin plasma concentrations have been observed during chronic leuprorelin acetate for depot suspension 7.5 mg administration, but testosterone levels appear to be maintained at castrate levels.
Leuprorelin Acetate for Depot Suspension 3.75 mg

Serum levels of leuprorelin acetate 3.75 mg were measured in 11 patients with pre-menopausal breast cancer over 12 weeks. Mean leuprorelin 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 drug accumulation.
Leuprorelin Acetate for Depot Suspension - 3 Month 11.25 mg

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 four, a mean leuprorelin plasma concentration of 0.26 (± 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 – 3 month 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 ± 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%.

Metabolism

In healthy male volunteers, a 1 mg bolus of leuprorelin acetate administered intravenously revealed that the mean systemic clearance was 7.6 L/hour, with a terminal elimination half-life of approximately three hours based on a two-compartment model.

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

The major metabolite (M-I) plasma concentrations measured in five prostate cancer patients given leuprorelin acetate depot reached 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 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 the leuprorelin acetate in hepatic and renal impaired patients has not been determined.

5.3 Preclinical safety data
In male rats, reduced fertility and chromosomal damage in gametes have been reported.

Carcinogenicity

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the medicine was administered subcutaneously at high daily doses (0.6 to 4 mg/kg/day). This study also revealed a significant but not a dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males in (highest incidence in the low dose group). In mice, no leuprorelin acetate-induced tumours or pituitary abnormalities were observed at a dose as high as 60 mg/kg/day for two years. Patients have been treated with leuprorelin acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity

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

Reproduction toxicity

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024 and 0.024 mg/kg (1/600 to 1/6 the adult dose, 1/1200 to 1/12 of the human paediatric dose) to rabbits, Lectrum ® 3.75 mg produced a dose related increase in major foetal abnormalities. Similar studies in rats failed to demonstrate an increase in foetal malformations. There was increased foetal mortality and decreased foetal weights with the two higher doses of Lectrum ® 3.75 mg in rabbits and with the highest dose (0.024 mg/kg) in rats.

The effects on foetal mortality are logical consequences of the alterations in hormonal levels brought about by this medicine. Therefore, a possibility exists that spontaneous abortion may occur if the medicine is administered during pregnancy.

6. Pharmaceutical particulars

6.1 List of excipients

Gelatin, Poly (lactic-glycolic) acid 75:25, Mannitol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store over 30° C in a dry place protected from heat.
Injection should not be used if container is leaking, or it contains undissolved particles.
Protect from direct sun light, freezing and heat.
Keep medicine out of reach of children.

6.5 Nature and contents of container

Each carton of Lectrum contains:

1 vial of sterile hydrolyzed powder for injection with diluent ampoule.

Pack size: Lectrum 3.75mg Injection 1's.

6.6 Special precautions for disposal and other handling

- Do not dispose of unused medicine via wastewater, household waste, drains or sewerage systems (e.g. Toilets)
- Return all unused medicine to your pharmacist
- **To be sold on the prescription of a registered medical practitioner only.**

7. MARKETING AUTHORIZATION / REGISTRATION HOLDER

Product license Holder & Drug Product Manufacturer:
M/s Eriochem S.A., Ruta 12, KM 452(3107) Colonia Avellaneda, Departmento Parana, Provincia Entre Rios, Republica, Argentina.

Marketing Authorization Holder in Pakistan
M/s AGP Limited
Address: B-23-C, S.I.T.E., Karachi
Fax: +9221 32570678
E-mail: info@agp.com.pk

MANUFACTURER(S)

Name of Manufacturing site	Address of site	Manufacturing step (if applicable)
M/s Eriochem S.A.	Ruta 12, KM 452(3107) Colonia Avellaneda, Departmento Parana, Provincia Entre Rios, Republica, Argentina.	-

8. REGISTRATION NUMBER / MARKETING AUTHORISATION NUMBER

Registration number: 115758

9. Date of first authorisation/renewal of the authorisation

Date of first Registration / Market Authorization: 9th May 2024

Date of latest renewal: N/A