SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

1.1. Product name

Luprodex 3.75 mg (Depot)

Leuprolide Acetate for Injection 3.75 mg (Depot)

1.2. Strength

3.75 mg / vial

1.3. Pharmaceutical dosage form

Lyophilized Powder for Injection

2. Qualitative and Quantitative compositions

Pack Size: 5 ml

Composition	**Quantity /vial**	**Reference to Standards**	**Function**
A. Drug Solution			
Leuprorelin (As Acetate)	3.75 mg	B.P.	Active pharmaceutical ingredient
Methanol*	q.s	B.P.	Solvent for API
Sodium Chloride*	q.s	B.P.	Processing aid
B. Non-Aqueous polymer phase			
PLGA biodegradable polymer	33.75 mg	I.H.	Bio-eroding polymer to control release
Dichloromethane*	--	B.P.	Solvent for polymer
C. Aqueous phase for Emulsion			
Polyvinyl Alcohol*	--	B.P.	Emulsifier
Water for Injection*	--	B.P.	Solvent for Polyvinyl Alcohol
D. Solution for Lyophilization			
Mannitol (Low endotoxin <1 IU/mg)	6.6 mg	B.P.	Cryoprotectant
Water for Injection*	q.s	B.P.	Solvent for Cryoprotectant

* Does not remain in the final product

B.P.: British Pharmacopoeia; I.H.: In House; q.s.: Quantity sufficient

3. Pharmaceutical form:

Lyophilized Powder for Injection (White to off white powder. Majority of particles are spherical when observed under optical microscope. On reconstitution uniform suspension is obtained which passes through the 22"gauge needle easily).

4. Clinical particulars:

4.1. Therapeutic Indications:

1. **Endometriosis**

Luprodex 3.75 mg (Depot) is indicated in the treatment of endometriosis, including pain relief and reduction of endometriosis lesions. Duration of initial treatment or retreatment should be limited to 6 months.

Luprodex 3.75 mg (Depot) can be used as sole therapy where it may provide symptomatic relief for women close to menopause who do not desire surgery, or as an adjunt to surgery.

2. Uterine Leiomyomata (Fibroids)

Luprodex 3.75 mg (Depot) concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. Luprodex 3.75 mg (Depot) may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with Luprodex 3.75 mg (depot) is up to six months.

3. Advanced Prostate Cancer (Palliative Treatment)

Luprodex 3.75 mg (Depot) is indicated in the treatment of advanced prostatic cancer when orchidectomy or estrogen administration are either not indicated or unacceptable to the patient.

4. Central Precocious Puberty (CPP)

Luprodex 3.75 mg (Depot) 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 8 years in girls and less than 9 years in boys.
2. Clinical diagnosis should be confirmed prior to initiation of therapy as follows: Confirmation of diagnosis by a pubertal response to a GnRH stimulation test and Bone age advanced one year beyond the chronological age.
3. Other evaluations and assessments should also include:
   - Height and weight measurements ▪ Sex steroid levels
   - Adrenal steroid level to exclude congenital adrenal hyperplasia. Beta HCG level to rule out a chorionic gonadotropin secreting tumour.
   - Computerized tomography of the head to rule out intracranial tumour.

4.2. Posology and method of administration

Luprodex 3.75 mg (Depot) must be administered under the supervision of a physician.

Endometriosis: The recommended duration of treatment with Luprodex 3.75 mg (Depot) as a single subcutaneous or intramuscular injection every month for a period of 6 months only. The initial dose should be given during the first 5 days of menstrual cycle.

In women, the addition of hormone replacement therapy (estrogen and progestogen) would be useful to reduce bone mineral density loss and vasomotor symptoms.

Uterine Leiomyomata (Fibroids): Recommended duration of therapy with Luprodex 3.75 mg (Depot) is for 3-4 months and maximum up to 6months. The initial dose should be given during the first 5 days of menstrual cycle. For endometrial preparation prior to intrauterine surgery, 3.75 mg leuprorelin acetate single dose may be given subcutaneous or intramuscular injection 5-6 weeks prior to surgery.

Prostate cancer: Administered monthly as a single intramuscular injection of 3.75 mg depot every month. Therapy should not be discontinued when remission or improvement occurs. This treatment is usually continued upon development of castrate-resistant prostate cancer.

Central Precocious Puberty (CPP):

Luprodex 3.75 mg (Depot) must be administered under the supervision of a paediatrician.

The starting dose is based on the body weight of the child

Children ≥ 20 kg of weight:

1 ml (3.75 mg leuprorelin acetate) suspension of 44.1 mg in 1 ml vehicle solution are administered once a month as a single subcutaneous injection.

Children < 20 kg of weight:

In these rare cases the following dosage should be administered according to the clinical activity of the central precocious puberty:

0.5 ml (1.88 mg leuprorelin acetate) is administered once a month as a single subcutaneous injection.

The remainder of the suspension should be discarded. The child's weight gain should be monitored.

Depending on the activity of the central precocious puberty, it may be necessary to increase the dosage in the presence of inadequate suppression (clinical evidence e.g. spotting or inadequate gonadotropin suppression in the LHRH test).

It is recommended to use the lowest volumes possible for injections in children in order to decrease the inconvenience due to injection.

The duration of treatment depends on the clinical parameters at the start of treatment or during the course of treatment (final height prognosis, growth velocity, bone age and/or bone age acceleration) and is decided by the treating paediatrician together with the legal guardian and, if appropriate, the treated child.

In girls with bone maturation of older than 12 years and boys with bone maturation of older than 13 years discontinuation of treatment should be considered taking into account the clinical parameters.

The administration interval should be 30 ± 2 days in order to prevent the recurrence of precocious puberty symptoms.

4.3. Reconstitution & Administration for Luprodex 3.75 mg (Depot)

Use Aseptic precautions throughout

Do not substitute saline or sterile water for diluent .

1. Ensure that the diluent fluid is at bottom section of the ampoule of diluent. Open the ampoule from the tip.
2. Using a syringe with 22 gauge needle, withdraw 1 ml of diluent from the ampoule. (Extra Diluent is provided, any remaining unused portion should be discarded)
3. Remove the plastic seal cap from the vial.
4. Inject the Diluent from the syringe into the glass vial.
5. Shake well for thorough dispersion of particles to obtain uniform suspension. (The suspension will appear milky)
6. Withdraw entire contents from the vial into the syringe.
7. Inject intramuscularly / subcutaneously.
8. Discard the unused product remaining in the vial along with unused diluent remaining in the ampoule.

The product has been shown to be stable for 24 hours following reconstitution. Since the product does not contain a preservative, the reconstituted product should be discarded if not used immediately.

4.4. Contra-indications

1. Hypersensitivity to GnRH, GnRH agonist analogs or its diluent.
2. Undiagnosed abnormal vaginal bleeding.
3. Luprodex 3.75 mg (Depot) is contraindicated in women who are pregnant while receiving the drug. Luprodex 3.75 mg (Depot) may cause fetal abnormalities when administered to a pregnant woman.

4. Use in women who are breast feeding.

4.5. Special warning and precautions for use

Cardiovascular disease: 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 (see section 4.5) physicians should assess the benefit risk ratio. 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.

Androgen deprivation therapy may prolong the QT 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 (see section 4.5) physicians should assess the benefit risk ratio.

Transient testosterone flare: Leuprorelin acetate causes a transient increase in serum concentrations of testosterone, dihydrotestosterone and acid phosphatase during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, haematuria, or ureteral or bladder outlet obstruction. These symptoms usually subside on continuation of therapy.

Bone density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with GnRH agonists. The risk for fractures owing to osteoporosis is generally higher than the risk for pathological fractures.

Pituitary apoplexy have been reported after the administration of GnRH-agonists and was presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention is required.

Hyperglycemia and diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported after receiving GnRH agonists.

Convulsions: Post marketing reports of convulsions have been observed in patients on leuprorelin acetate with or without a history of predisposing factors.

Hepatic dysfunction and jaundice with elevated liver enzyme have been reported. Therefore, close observation should be made and appropriate measures taken if necessary.

Spinal fracture, paralysis and hypotension have been reported.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as leuprorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

When considering the preoperative treatment of fibroids it is mandatory to confirm the diagnosis of fibroids and exclude an ovarian mass, either visually by laparoscopy or by ultrasonography or other investigative technique, as appropriate, before administering leuprolide acetate.

The patients should be warned of severe bleeding following the administration of leuprolide acetate as a consequence of the acute degeneration of the fibroids.

Leuprolide acetate may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedure.

Precautions

Men: Patients with urinary obstruction and patients with metastatic vertebral lesions should begin Leuprolide acetate therapy under close supervision for the first few weeks of treatment.

Women: Since menstruation should stop with effective doses of Leuprolide acetate, the patient should notify her physician if regular menstruation persists.

In girls with central precocious puberty: Before starting the therapy, a precise diagnosis of idiopathic and/or neurogenic central precocious puberty is necessary.

4.6. Interaction with other drugs, other forms of interactions:

Studies for interaction with drugs or any other forms of interactions have not been done.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Leuprolide 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.

Low HDL-cholesterol (<40mg/dL) and elevated LDL-cholesterol (>160 mg/dL) are recognized risk factors for cardiovascular disease. The long term significance of the observed treatment related changes in serum lipids in women with endometriosis is unknown. Therefore, assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with Luprodex 3.75 mg (Depot) and norethindrone acetate.

If additional treatment (duration longer than 3 months) with Luprodex 3.75 mg (Depot) is contemplated, bone density should be assesses prior to initiation of therapy to ensure that values are within normal limits.

Pediatric Use: Experience with Luprodex 3.75 mg (Depot) for treatment of endometriosis has been limited to women 18 years of age and older.

4.7. Use in pregnancy and lactation

Safe use of Leuprorelin Acetate in pregnancy has not been established clinically.

Studies in animals have shown reproductive toxicity. Before starting treatment with Luprorelin Acetate, pregnancy must be excluded. There have been reports of foetal malformation when Luprorelin Acetate has been given during pregnancy.

Luprorelin Acetate should not be used in women who are breastfeeding.

When used 3-monthly at the recommended dose, Luprorelin Acetate usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking Luprorelin Acetate and therefore patients should use non-hormonal methods of contraception during treatment.

Patients should be advised that if they miss successive doses of Luprorelin Acetate, breakthrough bleeding or ovulation may occur with the potential for conception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatinent, the drug must be discontinued. The patient must bc apprised of this evidence and the potential for an unknown risk to the foetus.

4.8. Effects on ability to drive and operate machine

Luprodex 3.75 mg (Depot) can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.9. Undesirable effects

Adverse events are mainly subject to the specific pharmacological action of leuprorelin acetate, namely increases and decreases in certain hormone levels. The most commonly reported adverse reactions are hot flashes, nausea, malaise and fatigue and transient local irritation at the site of injection. Mild hot flashes occur in approximately 58% of patients.

The following adverse events are from literature. Adverse events are classified, by frequency, as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), and very rare (<1/10,000), not known (cannot be estimated from the available data).

Very Common	fatigue, injection site burning, injection site paraesthesia, hot flashes, ecchymoses, erythema
Common	Nasopharyngitis, nausea, diarrhoea, gastroenteritis/colitis, pruritus, night sweats, arthralgia, limb pain, myalgia, rigors, weakness, urinary infrequency, difficulty in micturation, dysuria, nocturia, oliguria, breast tenderness, testicular atrophy, testicular pain infertility, breast hypertrophy, erectile dysfunction, reduced penis size, Malaise, injection site pain, injection site bruising, injection site stinging, increased blood creatinine phosphokinase, prolonged coagulation time, hematology changes, anaemia
Uncommon	urinary tract infection, local skin infection, aggravated diabetes mellitus, abnormal dreams, depression, decreased libido, dizziness, headache, hypoaesthesia, insomnia, taste disturbance, smell disturbance, vertigo, hypertension, hypotension, constipation, dry mouth, dyspepsia ,vomiting rhinorrhoea, dyspnoea, clamminess,

	increased sweating, back pain, muscle cramps, bladder spasm, haematuria, aggravated urinary frequency, urinary retention, gynaecomastia, impotence, testicular disorder, injection site pruritus, injection site induration, lethargy, pain, pyrexia, increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time, increased weight
Rare	abnormal involuntary movements, syncope, collapse, flatulence, eructation, alopecia, skin eruption, breast pain, injection site ulceration
Very Rare	injection site necrosis
Not Known	QT prolongation (see sections 4.4 and 4.5)

Other adverse events which have been reported in general are : peripheral oedema, pulmonary embolism, palpitations, myalgia, muscle weakness, an alteration in the skin sensation, chills, rash, amnesia and visual disturbances, muscular atrophy, pituitary apoplexy, thrombocytopenia, leucopenia, convulsions. Decreased bone density has been reported in literature who have been treated with GnRH analogues.

In men cases where a "tumour flare" occurs after leuproline acetate therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia. These symptoms subside on continuation of therapy.

In women, adverse events are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness. Estrogen levels return to normal after treatment is discontinued.

4.10. Overdoses

No cases of overdose has been reported.

In animal studies, like in rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnoea, decreased activity and local irritation at the injection site. In early clinical trials using daily subcutaneous Leuprolide Acetate in patients with prostate cancer, doses as high as 20 mg/day for upto two years caused no adverse effects differing from those observed with the 1 mg/day dose. In cases of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

5. Pharmacological properties: Pharmacotherapeutic group: Gonadotropin releasing hormone analogues.

ATC code: L02A E02

Leuprolide acetate is a synthetic nonapeptide agonist of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses ovarian and testicular steroid secretion.

5.1. Pharmacodynamic properties

Administration of Leuprolide acetate results in an initial increase in circulating levels of luteinising hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids, both in females and males. Continuous administration of Leuprolide acetate results in decreased levels of LH and FSH. In men serum testosterone levels, initially raised in response to early luteinising hormone (LH) release, fall to castrate levels in about 2-4 weeks. Estradiol levels will decrease to postmenopausal levels in premenopausal women within one month of initiating treatment.

No pharmacodynamics studies have been conducted for Luprodex. From the literature following data were obtained.

Leuprolide acetate when administered in males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL). These decreases occur within three to five weeks after initiation of treatment. In a study, mean testosterone levels at six months was 10.1 (± 0.7) ng/dL, comparable to levels following bilateral orchiectomy. All patients who received the full dose of 22.5 mg Leuprolide in the reached castrate levels at 5 weeks; 99 % had reached this by day 28. In the vast majority of patients the testosterone levels seen were below 20 ng/dL. Prostate specific antigen (PSA) levels decreased by 98% over six months.

A study compared the efficacy and safety of the 3.75 mg and 11.25 mg depots of Leuprolide acetate in advance and metastatic prostate cancer. Mean serum testosterone level fell below the threshold for chemical castration (0.5 ng/ml) at one month of treatment, continuing to decrease thereafter and stabilising at a value below the castration threshold. The decline in serum PSA mirrored that of serum testosterone in both groups. Long-term studies have shown that continuation of therapy maintains testosterone below the castrate level for up to seven years, and presumably indefinitely.

A long-term efficacy and safety of Leuprolide acetate was assessed in patients with metastatic prostate cancer. Testosterone levels were maintained below the castrate threshold over the 63-month follow up period. Median survival time exceeded 42.5 months for those receiving monotherapy and 30.9 months for those receiving Leuprolide acetate in combination with anti-androgens (this difference relating to baseline differences between groups)

5.2. Pharmacokinetic properties

Leuprolide Acetate is not active when given orally.

Absorption: Intramuscular injection of the depot formulation provides plasma concentrations of Leuprolide over a period of one month.

Distribution: Distributed to kidney, liver, pineal and pituitary tissues.

Metabolism: It is metabolized to its metabolites in hypothalamus and anterior pituitary gland.

Elimination: Leuprolide is eliminated by enzymatic breakdown and renal excretion.

No pharmacokinetic studies have been conducted for Luprodex

Literature data indicates that Leuprolide acetate is well absorbed after subcutaneous and intramuscular injections. Leuprolide acetate binds to the LHRH receptors and is rapidly degraded. An initially high plasma level of Leuprolide acetate peaks at around 3 hours after a subcutaneous injection, followed by a decrease to maintenance levels in 7 to 14 days. Leuprolide acetate provides continuous plasma levels for up to 117 days resulting in suppression of testosterone to below castration level within 4 weeks of the first injection in the majority of patients. The metabolism, distribution and excretion of Leuprolide acetate in humans have not been fully determined.

A study which included 3.75, 7.5, 11.25, 15 and 30 mg depots of Leuprolide Acetate showed that a mean Cmax of 13.1, 20.8 to 21.8, 47.4, 54.5 and 53 mcg/L, respectively, occur within 1 to 3 hours of depot subcutaneous administration. The plasma concentration was maintained between 0.4 and 1.4 mcg/L over 28 days after single 3.75, 7.5 or 15mg depot injections.

A significant dose-related increase in the AUC from 0 to 35 days was noted after depot injection of Leuprolide 3.75, 7.5 and 15mg. Mean volume of distribution of Leuprolide is was 36, 33 and 27L after depot administration of 3.75, 7.5 and 15mg, respectively. Total body clearance is 9.1 L/h and elimination half-life 3.6 hours after a subcutaneous 1mg injection; corresponding values after intravenous injection are 8.3 L/h and 2.9 hours.

In Children: The Leuprolide serum levels in children during the first 6 months of treatment following s.c. administration of Leuprolide acetate 3-month depot (two injections) showed following results.

From the first injection, the Leuprolide serum levels increase reaching maximal serum levels at month 4 (294.79 pg/ml ± 105.42) and slightly decrease until month 6 (229.02 pg/ml ± 103.33).

6. Pharmaceutical particulars:

6.1. List of Excipients:

Methanol, Sodium Chloride, PLGA biodegradable polymer, Dichloromethane, Polyvinyl Alcohol, Mannitol, Water for Injection.

6.2. Incompatibilities:

Not Applicable

6.3. Shelf-life:

36 months from the date of manufacturing.

6.4. Special precaution for storage:

Store below 30°c. Do not freeze.

6.5. Nature and contents of container:

Luprodex 3.75 mg (Depot) is available as Sterile Lyophilized powder for Injection. Each carton of Luprodex 3.75 mg (Depot) contains one PVC tray. One PVC tray contains one 5 ml labeled vial, 2 ml Diluent Labelled Ampoule, two filter Needles, two alcohol swabs, one syringe and one pack insert.

7. Marketing authorization holder:

Bharat Serums & Vaccines Ltd.
3rd Floor, Liberty Tower, Plot No. K-10,
Behind Reliable Plaza, Kalwa Industrial Estate,
Airoli, Navi Mumbai 400708

8. Marketing authorization number:

FDA-HBP-MA-0101

9. Date of first authorization / renewal of authorization:

10/12/2023

10. Date of revision of the text:

Not Applicable