SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

1.1. Product name

Luprodex 11.25 mg (Depot)

Leuprolide Acetate for Injection 11.25 mg (Depot)

1.2. Strength

11.25 mg / vial

1.3. Pharmaceutical dosage form

Lyophilized Powder for Injection

2. Qualitative and Quantitative composition

Pack Size: 5 ml vial

Leuprorelin (As Acetate) 11.25

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

3. Pharmaceutical form:

Before Reconstitution: White to off white powder

After Reconstitution: On reconstitution, white uniform suspension is obtained, which passes through the 22"gauge needle easily.

4. Clinical particulars:

4.1. Therapeutic Indications:

1. Endometriosis

Luprodex 11.25 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 11.25 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 adjunct to surgery.

2. Uterine Leiomyomata (Fibroids)

Luprodex 11.25 mg (Depot) concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by

uterine leiomyomata. Luprodex 11.25 mg (Depot) may be added if the response to iron alone is considered inadequate.

Recommended duration of therapy with Luprodex 11.25 mg (depot) is upto six months.

3. **Advanced Prostate Cancer (Palliative Treatment)**

Luprodex 11.25 mg (Depot) is indicated in the treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchidectomy or estrogen administration are either not indicated or unacceptable to the patient.

4.2. Posology and method of administration

Luprodex 11.25 mg (Depot) must be administered under the supervision of a physician.

Endometriosis: The recommended duration of treatment with Luprodex 11.25 mg (Depot) alone or in combination with norethindrone acetate is six months. The choice of Luprodex 11.25 mg (Depot) alone or Luprodex 11.25 mg (Depot) plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the healthcare professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to or Luprodex 11.25 mg (Depot) alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six months course of Luprodex 11.25 mg (Depot) three monthly and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-months course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Luprodex 11.25 mg (Depot) alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.

An assessment of cardiovascular risk factors such as cigarette smoking is recommended before beginning treatment with Luprodex 11.25 mg (Depot) and norethindrone acetate.

Uterine Leiomyomata (Fibroids): Recommended duration of therapy with Luprodex 11.25 mg (Depot) is for 3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with Luprodex 11.25 mg (Depot) Is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

Prostate cancer: Administered monthly as a single intramuscular injection. Therapy should not be discontinued when remission or improvement occurs.

4.3. Reconstitution & Administration for Luprodex 11.25 mg (Depot)

Use Aseptic precautions throughout

Do not substitute saline or sterile water for diluent

1. Ensure that the diluent fluid is at the bottom section of the ampoule of diluent. Open the ampoule from the tip.
2. Using a syringe with 22-gauge needle, withdraw 1.5 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 the 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 11.25 mg (Depot) is contraindicated in women who are pregnant while receiving the drug. Luprodex 11.25 mg (Depot) may cause foetal harm when administered to a pregnant woman.
4. Use in women who are breast feeding.

4.5. Special warning and precautions for use

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with Luprodex 11.25 mg (Depot), pregnancy must be excluded.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

Monitoring in Advanced Prostatic Cancer Patients:

Closely observe Prostatic Cancer Patients with metastatic vertebral lesions or with urinary tract obstruction during first few weeks of therapy. Monitor therapeutic response by measuring testosterone serum levels, prostate-specific antigen (PSA), and prostatic acid phosphatase. Verify down-regulation in patients whose weight has increased significantly while on therapy.
Monitor measurements of bone age for advancement every 6 to 12 months.

Worsening of signs or symptoms during the first weeks of treatment have been reported. Worsening of symptoms 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 treatment.

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

Administration of Luprodex 11.25 mg (Depot) in therapeutic doses 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 upto three months after discontinuation of Luprodex 11.25 mg (Depot) may be misleading.

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 11.25 mg (Depot) and norethindrone acetate.

If additional treatment (duration longer than 3 months) with Luprodex 11.25 mg (Depot) is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

Pediatric Use: Experience with Luprodex 11.25 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.

Luprodex 11.25 mg (Depot) is contraindicated in women who are breast feeding and in women who are pregnant while receiving the drug. Luprodex 11.25 mg (Depot) may cause foetal harm when administered to a pregnant woman.

4.8. Effects on ability to drive and operate machine

Luprodex 11.25 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 micturition, 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 have 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.

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

Leuprolide Acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation of gonadotropins, chronic stimulation with Leuprolide Acetate results in suppression or "down-regulation" of these hormones and consequent suppression of ovarian and testicular steroidogenesis. These effects are reversible on discontinuation of drug therapy.

Leuprolide Acetate is not active when given orally.

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. When used three-monthly at the recommended dose, Luprodex 11.25 mg (Depot) usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking Luprodex 11.25 mg (Depot). Therefore, patients should use non-hormonal methods of contraception.

Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the foetus.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic 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.

6. Pharmaceutical particulars:

6.1. List of Excipients:

Excipients	Pharmacological claim
Poly (D, L) Lactide-	I.H.
Mannitol	B.P.

B.P.: British Pharmacopoeia;

I.H.: In-house

6.2. Incompatibilities:

Not Applicable

6.3. Shelf-life:

36 months from the date of manufacturing.

6.4. Special precaution for storage:

Store below 25^{o}C. Do not freeze. Protect from light. Keep out of reach of children.

6.5. Nature and contents of container:

Each pack of Luprodex (Depot) 11.25 mg is supplied as one vial containing microspheres equivalent to 11.25 mg of Leuprolide Acetate along with one ampoule of diluent for reconstitution, one disposable syringe, two needles and two alcohol swabs.

7. Marketing authorization holder:

Bharat Serums & Vaccines Ltd.
17th Floor, Hoechst House,
Nariman Point,
Mumbai — 400 021
India.

8. Marketing authorization number:

H2022/CTD10061/20389

9. Date of first authorization / renewal of authorization:

Not Applicable

10. Date of revision of the text:

23/08/2026