For the use only of Physician, Gynaecologist, Oncologist,
Endocrinologist, Hospital or Laboratory

Leuprolide Acetate for Injection 3.75mg (Depot)

LUPRODEX™

3.75 mg (DEPOT)

(1 month Depot)
Lyophilized

For I.M. / S.C. Use
Single Dose Vial
Not for Intravenous Administration

DESCRIPTION:
LUPRODEX™ 3.75 mg (DEPOT) is a sterile lyophilized powder containing Leuprolide Acetate formulated as Microspheres. **LUPRODEX**™ 3.75 mg (DEPOT) is to be reconstituted with accompanying diluent which forms a uniform suspension, intended for intramuscular or subcutaneous injection to be administered once every month.

Leuprolide Acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone.

COMPOSITION:
1. **LUPRODEX**™ 3.75 mg (DEPOT):
Each vial contains (As lyophilized powder):
Leuprorelin B.P. (As acetate) ..... 3.75 mg
Excipients : Poly (D,L-lactide-co-glycolide) Biodegradable
Polymer, Gelatin I.P., D-Mannitol I.P.

2. Ampoule of diluent for reconstitution:
Each mL contains:
D-Mannitol I.P. 50mg
Water for Injection I.P. ..... q.s.
Other Excipients: Sodium Carboxymethyl Cellulose I.P. as a suspending agent and Polysorbate-80 as a wetting agent.

CLINICAL PHARMACOLOGY:
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.

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 into its metabolites in hypothalamus and anterior pituitary gland.

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

When used monthly at the recommended dose, **LUPRODEX**™ 3.75 mg (DEPOT) usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking **LUPRODEX**™ 3.75 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 fetus.

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.

INDICATIONS AND USAGE:
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 adjunct to surgery.

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.

Advanced Prostate Cancer (Palliative Treatment):
LUPRODEX™ 3.75 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.

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 evaluation 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 tumor.
≥ Pelvic / adrenal / testicular ultrasound to rule out a steroid secreting tumor.
≥ Computerized tomography of the head to rule out intracranial tumor.

CONTRAINDICATIONS:
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 harm when administered to a pregnant woman.

4. Use in women who are breast-feeding.

SIDE EFFECTS & ADVERSE REACTIONS:
'Flare phenomenon' is the commonly occurring side effect of Leuprolide (symptoms of hot flushes; sweats; peripheral oedema; GI upset). Temporary increase in the degree of bone pain and obstructive voiding symptoms have been noted within the first 72 hours of therapy. This may occur due to increased testosterone level during the first week of treatment. Concomitant administration of an androgen antagonist like flutamide prevents the flare phenomenon in male patients.

Long Term usage leading to decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the non- treated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Anaphylactoid or asthmatic process have been rarely reported.
Rash, urticaria, and photosensitivity reactions have also been reported.
Also a localized reaction including induration and abscess at the site of injection.
Symptoms consistent with fibromyalgia (eg: joint and muscle pain, headaches, sleep disorder, gastrointestinal distress, and shortness of breath) have been reported.
Other reactions reported are:
≥ Cardiovascular System - Hypotension, Pulmonary embolism;
≥ Blood & Lymphatic System - Decreased WBC;
≥ Nervous System - Peripheral neuropathy, Spinal fracture / paralysis;
≥ Musculoskeletal System - Tenosynovitis like symptoms;
≥ Urogenital System - Prostate pain.

PRECAUTIONS & WARNINGS:
Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with **LUPRODEX**^{TM} 3.75 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 to12 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.

Drug / Laboratory Test Interactions:
Administration of **LUPRODEX**^{TM} 3.75 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 up to three months after discontinuation of **LUPRODEX**^{TM} 3.75 mg (DEPOT) may be misleading.

Low HDL-cholesterol (<40 mg/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 assessed 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 men and women 18 years of age and older.

DOSAGE AND 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) alone or in combination with norethindrone acetate is six months. The choice of **LUPRODEX**™ 3.75 mg (DEPOT) alone or **LUPRODEX**™ 3.75 mg (DEPOT) plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to **LUPRODEX**™ 3.75 mg (DEPOT) alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six month course of **LUPRODEX**™ 3.75 mg (DEPOT) monthly and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. **LUPRODEX**™ 3.75 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**™ 3.75 mg (DEPOT) and norethindrone acetate.

Uterine Leiomyomata (Fibroids): Recommended duration of therapy with **LUPRODEX**™ 3.75 mg (DEPOT) is up to 3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with **LUPRODEX**™ 3.75 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.

Central Precocious Puberty (CPP): The dose of **LUPRODEX**™ 3.75 mg (DEPOT) must be individualized for each child. The dose is based on a mg/kg ratio of drug to body weight. Younger children may require higher doses on a mg/kg ratio.

After 1-2 months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, sex steroids, and Tanner staging to confirm down regulation. Measurements of bone age for advancement should be monitored every 6-12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters.

The first dose found to result in adequate down regulation can probably be maintained for the duration of therapy in most children. However, there are insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate down regulation be verified in such patients whose weight has increased significantly while on therapy.

Discontinuation of **LUPRODEX**^{TM} 3.75 mg (DEPOT) should be considered before age 11 for girls and age 12 for boys.

The recommended starting dose is 0.3 mg/kg/4 weeks (minimum 7.5 mg) administered as a single intramuscular injection or subcutaneously. The starting dose will be dictated by the child's weight as follows:

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

It total down regulation is not achieved; the dose should be titrated upward in increments of 3.75 mg every 4 weeks. This dose will be considered the maintenance dose.

When two injections are required to achieve the desired total dosage, they should be administered at one site, however **more than two** injections should be administered at different injection sites.

Reconstitution & Administration for LUPRODEX^{TM} 3.75 mg (DEPOT):

- **Use Aseptic Precautions throughout.**
- **Do not substitute saline or sterile water for diluent.**

(please refer diagram for the reconstitution details on the back side).

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 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 a 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.

OVERDOSAGE:

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials using daily subcutaneous Leuprolide Acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1mg/day dose.

STORAGE:

Store below 25^{0}C. Protect from light. Do not freeze.

PRESENTATION:
Each pack of **LUPRODEX**™ 3.75 mg (DEPOT) is supplied as one vial containing microspheres equivalent to 3.75mg of Leuprolide Acetate along with one ampoule of diluent for reconstitution, one disposable syringe, two needles and two alcohol swabs.

REFERENCES:

i) Sean C. Sweetman, Martindale : The Complete Drug Reference,
34th Edition, 2005, The Pharmaceutical Press, 1331.

ii) Sennello LT, et al. Single dose pharmacokinetic of Leuprolide in humans following intravenous and subcutaneous administration.
J Pharm Sci 1986; 75:158-60.

iii) Takeuchi H, et al. A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis.
J Obstet Gynaecol Res 2000; 26:325-31.

iv) Hiroaki Okada, One- and three-month release injectable microspheres of the LH-RH superagonist leuprorelin acetate.
Adv Drug Del Rev 1997; 28:43-47.

v) Seidenfeld J, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systemic review and meta-analysis.
Ann Intern Med 2000; 132:566-77.

vi) Carel JC, et al. Treatment of central precocious puberty with depot leuprorelin.
Eur J Endocrinol 1995; 132:699-704.

Manufactured in India by :
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, Additional M.I.D.C., Ambernath (E) - 421 501

Procedure for Reconstitution:

LUPRODEX™

3.75 mg (DEPOT)

Use Aseptic Technique Throughout

Do not use Sterile Water for Injection or Sodium Chloride Injection (Saline) for reconstitution in place of the recommended diluent provided with this pack.

1) Visually inspect the vial. Vial should not be used if clumping or caking is evident. A thin layer of powder on the wall of the vial is considered normal. The diluent in the ampoule should appear clear.
Ensure that the fluid is at the bottom section of the ampoule (flick or tap lightly if need be).
Hold the ampoule and snap open the ampoule as shown in the picture.

2) Use luer lock syringe with 22 gauge needle provided with this pack.
Fix needle in luer lock till it rotates no more.
Withdraw 1ml of diluent from the ampoule.

3) Remove plastic seal cap of vial by flicking it off.

4) Inject diluent into the vial.

5) Shake well the contents of vial for thorough Dispersion.
The suspension will appear uniformly milky.

6) Withdraw entire contents of the vial back in the syringe.
Inject intramuscularly / subcutaneously.
Discard the remainder of the diluent, the ampoule and the vial.