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

Leuprolide Acetate for Injection 22.5 mg (DEPOT)

ल्युप्रोडेक्स
LUPRODEX® **(DEPOT)**
22.5 mg

(3 months Depot)
Lyophilized

For Intramuscular use
For Single use only
Not for Intravenous Administration

DESCRIPTION:

LUPRODEX™ (DEPOT) 22.5 mg is a sterile lyophilized powder containing Leuprolide Acetate formulated as Microspheres. **LUPRODEX™** (DEPOT) 22.5 mg is to be reconstituted with accompanying diluent which forms a uniform suspension, intended for intramuscular injection to be administered once every three months.

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™ (DEPOT) 22.5 mg:**
Each vial contains:
Leuprorelin B.P. (As acetate) ..... 22.5 mg
Excipients : Polylactic acid, Mannitol I.P.
2. **Ampoule of diluent for reconstitution:**
Each ml contains:
Mannitol I.P. ..... 50 mg
Water for Injection I.P. ..... q.s.
Other Excipients : Sodium Carboxymethyl Cellulose I.P., Polysorbate-80 I.P., Glacial acetic acid U.S.P.

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 three months.

PHARMACOKINETICS:

Absorption:
Following single injection of three month formulation of leuprolide acetate 22.5 mg in patients, mean peak plasma leuprolide concentration of 48.9ng/ml was observed at 4 hours and then declined to 0.67ng/ml at 12 weeks. Leuprolide appears to be released at constant rate following the onset of steady levels during the third week after the dosing, providing steady plasma concentration through the 12 week dosing interval.

However, intact leuprolide and inactive major metabolites could not be distinguished by the assay which was employed in the study. Detectable levels of leuprolide were present at all measurement points in all patients. The initial burst followed by rapid decline to steady state level, was similar to the release pattern seen with the monthly formulation.

Distribution:
The mean steady state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27L. in vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism:
In healthy male volunteers 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6L/h, with a terminal elimination half life of approximately 3 hours based on a two compartment model.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion:
Following administration of **LUPRODEX™** (DEPOT) 22.5 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations:
The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

INDICATIONS AND USAGE:

LUPRODEX™ (DEPOT) 22.5 mg 3 Months is indicated in the palliative treatment of advancedprostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

CONTRAINDICATIONS:

Hypersensitivity to GnRH, GnRH agonist analogs or its diluent.

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:

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.

Drug / Laboratory Test Interactions:
Administration of **LUPRODEX™** (DEPOT) 22.5 mg 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™** (DEPOT) 22.5 mg may be misleading.

PREGNANCY AND LACTATATION:

LUPRODEX™ (DEPOT) 22.5 mg is not meant for female.

DOSAGE AND ADMINISTRATION:

LUPRODEX™ (DEPOT) 22.5 mg must be administered under the supervision of an oncologist. **LUPRODEX™** (DEPOT) 22.5 mg should be administered by the intramuscular route.

The recommended dose of **LUPRODEX™** (DEPOT) 22.5 mg is one single injection administered every three months. Therapy should not be discontinued when remission or improvement occurs.

Reconstitution & Administration for LUPRODEX™ (DEPOT) 22.5 mg:

- **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 1.5 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. Remove the syringe / needle and keep aseptic.
6. Shake well for thorough dispersion of particles to obtain a uniform suspension. (The suspension will appear milky).

7. Withdraw entire contents from the vial into the syringe. Replace the needle with another sterile 22 guage needle provided with the pack.
8. Inject the entire content of syringe intramuscularly. The suspension settles very quickly following reconstitution; therefore, **LUPRODEX™** (DEPOT) 22 mg should be mixed and used immediately.
9. 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 1 mg/day dose.

STORAGE:
Store below 25°C. Do not freeze.

PRESENTATION:
Each pack of **LUPRODEX™** (DEPOT) 22.5 mg is supplied as one vial containing microspheres equivalent to 22.5 mg of Leuprolide Acetate along with one ampoule of diluent for reconstitution, one disposable syringe, two needles and two alcohol swabs.

To report Suspected Adverse Reactions, contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com/adverse.html

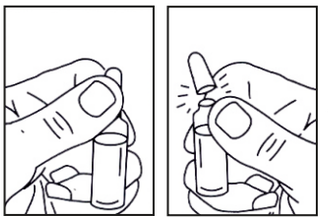
Manufactured in India by :
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, Additional M.I.D.C.,
Ambernath (E) - 421 501
IN90294D1

Procedure for Reconstitution:

ल्युप्रोडेक्स LUPRODEX® (DEPOT) 22.5 mg

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.



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- 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.

Use luer lock syringe with 22 gauge needle provided with this pack.

Fix needle in luer lock till it rotates no more.

Withdraw 1.5 ml of diluent from the ampoule.

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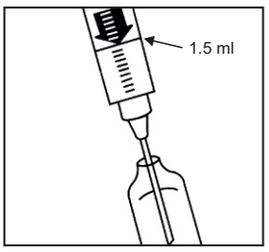

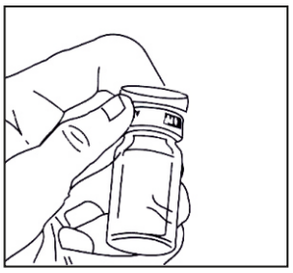

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- Remove plastic seal cap of vial by flicking it off.

Inject diluent into the vial.

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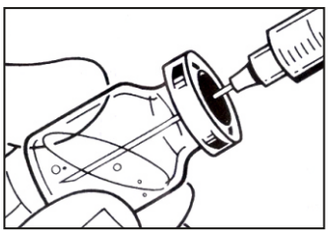

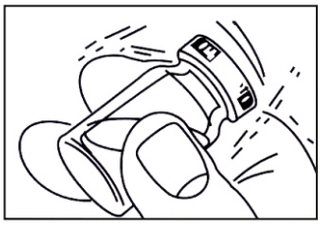

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- Shake well the contents of vial for thorough Dispersion.
- The suspension will appear uniformly milky.

Withdraw entire contents of the vial back in the syringe.

Inject intramuscularly.

Discard the remainder of the diluent, the ampoule and the vial.

6