

LEUPROLIDE ACETATE DEPOT- leuprolide acetate CIPLA USA INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEUPROLIDE ACETATE INJECTION safely and effectively. See full prescribing information for LEUPROLIDE ACETATE INJECTION.

**LEUPROLIDE ACETATE INJECTION DEPOT (leuprolide acetate for depot suspension).
Initial U.S. Approval: 2018**

INDICATIONS AND USAGE

LEUPROLIDE ACETATE INJECTION DEPOT is a gonadotropin-releasing hormone (GnRH) agonist indicated for:

- Palliative treatment of advanced prostatic cancer. (1)

DOSAGE AND ADMINISTRATION

Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule (2).

- LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3 months administration, given as a single intramuscular injection every 12 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

For Injection: 22.5 mg of leuprolide acetate in a single dose vial as a kit with a prefilled syringe containing diluent and a MIXJECT transfer device. (3)

CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist or any of the excipients in LEUPROLIDE ACETATE INJECTION DEPOT. (4).

WARNINGS AND PRECAUTIONS

- Tumor Flare: Increased serum testosterone (~50% above baseline) during first week of treatment; monitor serum testosterone and PSA. (5.6)
 - Isolated cases of transient worsening of symptoms, or additional signs and symptoms of prostate cancer during the first few weeks of treatment. (5.1)
 - A small number of patients may experience a temporary increase in bone pain which can be managed symptomatically. (5.1)
 - Isolated cases of ureteral obstruction and spinal cord compression have been reported with GnRH agonists, which may contribute to paralysis with or without fatal complications. (5.1)
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice (5.2)
- Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice. (5.3)
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong QT interval. Consider risks and benefits (5.4)
- Convulsions have been observed in patients with or without a history of predisposing factors. Manage convulsions according to the current clinical practice. (5.5)
- Monitor serum levels of testosterone following injection of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-month administration. (5.6)
- Embryo-Fetal Toxicity: LEUPROLIDE ACETATE INJECTION DEPOT may cause fetal harm. (5.7, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 10%) are hot flushes, upper respiratory infection, fatigue, diarrhea, pollakiuria, arthralgia, and injection site pain (6).

As with other GnRH agonist, other adverse reactions, including decreased bone density and rare cases of pituitary apoplexy may occur. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla at 1-866-604-3268 or FDA at 1-

USE IN SPECIFIC POPULATIONS

- Females and males of reproductive potential: LEUPROLIDE ACETATE INJECTION DEPOT may impair fertility. Counsel patients on pregnancy planning and prevention. (8.3)
- Pediatric: The use of LEUPROLIDE ACETATE INJECTION DEPOT formulations are not indicated for use in children (8.4)
- Geriatric: This label reflects clinical trials for LEUPROLIDE ACETATE INJECTION DEPOT in prostate cancer in which the majority of the subjects studied were at least 65 years of age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2018

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-month administration (leuprolide acetate) is indicated for palliative treatment of advanced prostate cancer.

2. DOSAGE AND ADMINISTRATION

2.1 LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-Month Administration

LEUPROLIDE ACETATE INJECTION DEPOT must be administered under the supervision of a physician.

In patients treated with GnRH analogues for prostate cancer, treatment is usually continued upon development of metastatic castration-resistant prostate cancer.

**Table 1. LEUPROLIDE ACETATE INJECTION DEPOT
Recommended Dosing**

Dosage	22.5 mg for 3-Month Administration
Recommended Dose	1 injection every 12 weeks

The recommended dose of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-month administration is one injection every 12 weeks. Do not use concurrently a fractional dose, or a combination of doses of this or any depot formulation due to different release characteristics.

Incorporated in a depot formulation, the lyophilized microspheres must be reconstituted and administered every 12 weeks as a single intramuscular injection.

2.2 Reconstitution Instructions for LEUPROLIDE ACETATE INJECTION DEPOT

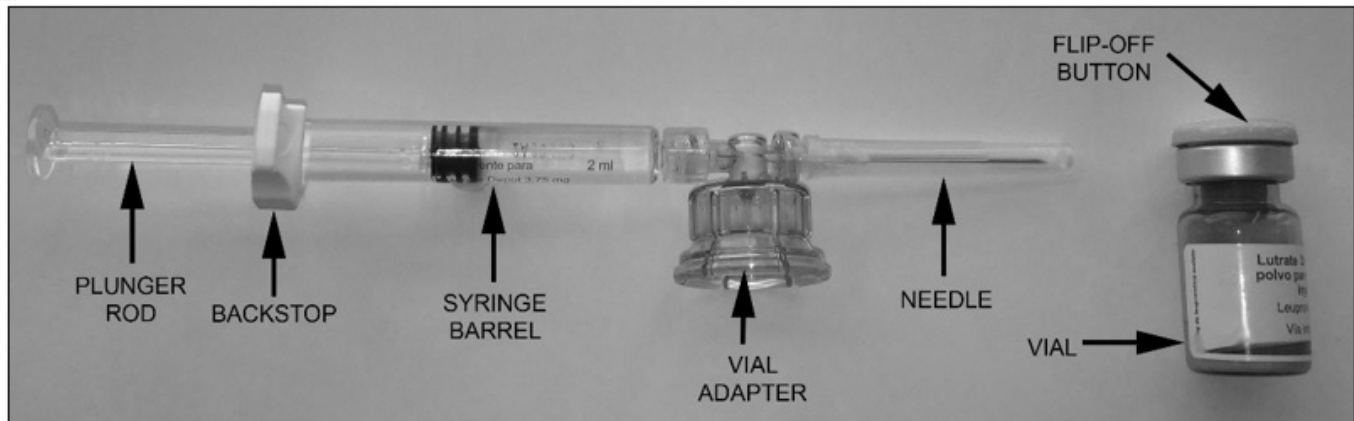
- Reconstitute and administer the lyophilized microspheres as a single intramuscular injection.
- The suspension should be administered immediately after reconstitution.
- As with other drugs administered by intramuscular injection, the injection site should be alternated periodically.
- Visually inspect LEUPROLIDE ACETATE INJECTION DEPOT powder (white to off-white powder). DO NOT USE the vial if clumping or caking is evident. A thin layer of powder

on the wall of the vial is considered normal prior to mixing with the diluent. The diluent contained in the prefilled syringe should appear clear and colorless.

- Use ONLY the provided diluent for reconstitution of LEUPROLIDE ACETATE INJECTION DEPOT. DO NOT use other diluents.
- The reconstituted product is a suspension of milky, white color appearance.

LEUPROLIDE ACETATE INJECTION DEPOT is packaged in a commercial kit. Each kit contains:

- One vial containing 22.5 mg of leuprolide acetate as lyophilized microspheres.
- One prefilled syringe containing 2 mL of mannitol for injection.
- One MIXJECT transfer device including one needle.



Please read the instructions completely before you begin.

MIXJECT Preparation

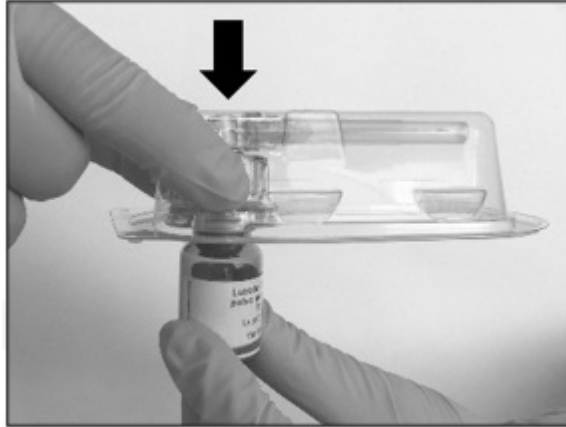
Wash your hands with soap and hot water and put on gloves¹ immediately prior to preparing the injection. Place the tray on a clean, flat surface that is covered with a sterile pad or cloth. Remove the MIXJECT device, the backstop, the prefilled syringe containing the solvent for reconstitution and the LEUPROLIDE ACETATE INJECTION DEPOT vial.

Remove the Flip-Off button from the top of the vial, revealing the rubber stopper. Place the vial in a standing upright position on the prepared surface. Disinfect the rubber stopper with the alcohol wipe. Discard the alcohol wipe and allow the stopper to dry.

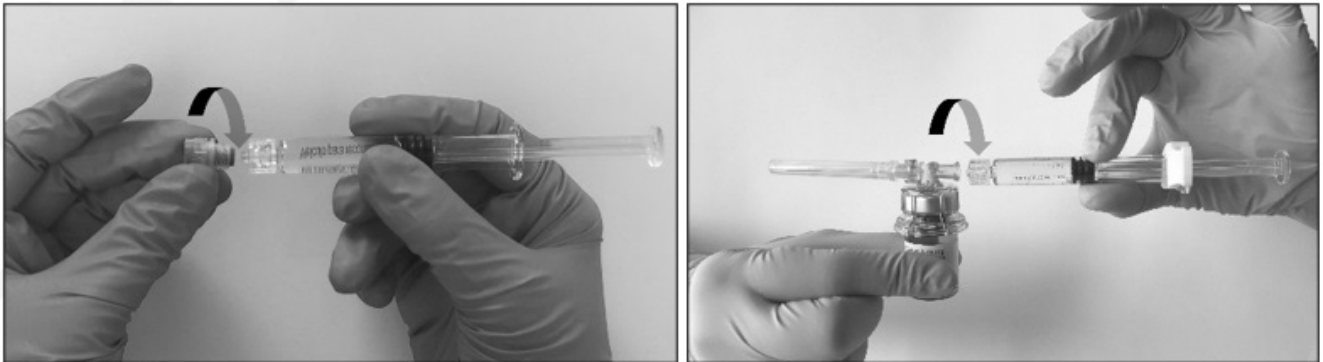
Insert the backstop to the flange of the syringe until you feel it snap in place. Proceed to MIXJECT Activation.

MIXJECT Activation

1. Peel the cover away from the blister pack containing the vial adapter (MIXJECT). **Do not remove the vial adapter from the blister pack.** Place the blister pack containing the vial adapter firmly on the vial top, piercing the vial. **Push down gently until you feel it snap in place.**



2. Remove the cap from the syringe barrel and then, **remove the blister pack from the vial adapter.** Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. Be sure to gently twist the syringe until it stops turning to ensure a tight connection.



3. While holding the vial, place your thumb on the plunger rod and push the plunger rod in all the way to transfer the diluent from the pre-filled syringe into the vial. Do not release the plunger rod.



4. **Keeping the plunger rod depressed, gently swirl the vial for approximately one minute until a uniform milky-white suspension is obtained.** This will ensure complete mixing of LEUPROLIDE ACETATE INJECTION and the sterile mannitol solution diluent. The suspension will now have a milky appearance. In order to avoid separation of the suspension, proceed to the next steps without delay.



5. Invert the MIXJECT system so that the vial is at the top. Grasp the MIXJECT system firmly by the syringe and pull back the plunger rod slowly to draw the reconstituted LEUPROLIDE ACETATE INJECTION into the syringe.



Return the vial to its upright position, and disconnect the vial adapter from the

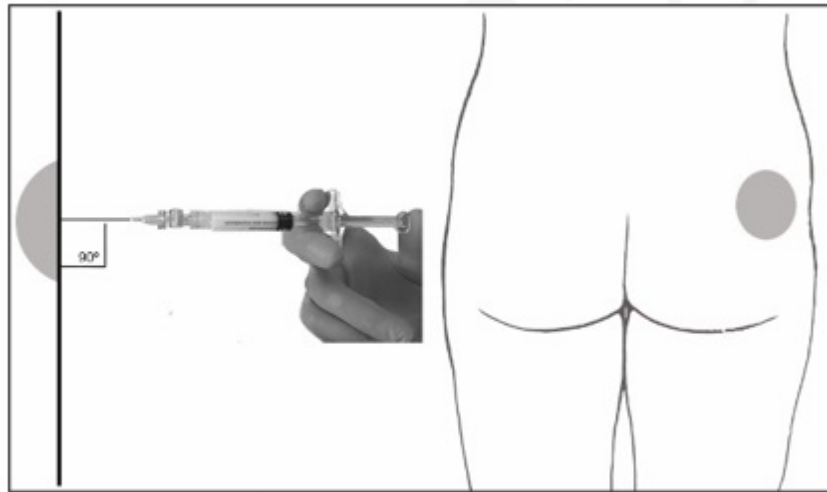
MIXJECT syringe assembly by grabbing firmly the syringe and turning the plastic cap of the vial adapter clockwise. **Grasp only the plastic cap when removing.**



6. Keep the syringe UPRIGHT. With the opposite hand pull the needle cap upward. Advance the plunger to expel the air from the syringe. The syringe containing LEUPROLIDE ACETATE INJECTION DEPOT suspension is now ready for administration. *The suspension should be administered immediately after reconstitution.*



7. After cleaning the injection site with an alcohol swab, administer the intramuscular injection by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated (see Figure).



NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock. If blood is present, remove the needle immediately. Do not inject the medication.

8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately discard the needle into a suitable sharps container. Dispose the syringe according to local regulations/procedures.

3. DOSAGE FORMS AND STRENGTHS

LEUPROLIDE ACETATE INJECTION DEPOT

For Injection: 22.5 mg of leuprolide acetate for 3-month administration as lyophilized microspheres in a single dose vial as a kit with a prefilled syringe containing 2mL 0.8% mannitol solution and a MIXJECT transfer device for a single dose injection.

4. CONTRAINDICATIONS

LEUPROLIDE ACETATE INJECTION DEPOT is contraindicated in:

- **Hypersensitivity**
LEUPROLIDE ACETATE INJECTION DEPOT is contraindicated in individuals with known hypersensitivity to GnRH agonists or any of the excipients in LEUPROLIDE ACETATE INJECTION DEPOT. Reports of anaphylactic reactions to GnRH agonists have been reported in the medical literature.

5. WARNINGS AND PRECAUTIONS

5.1 Tumor Flare

Initially, LEUPROLIDE ACETATE INJECTION DEPOT, like other GnRH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first weeks of treatment. Isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. Transient worsening of symptoms may develop. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

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

5.2 Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

5.3 Cardiovascular Diseases

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 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 a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

5.4 Effect on QT/QTc Interval

Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

5.5 Convulsions

Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Patients receiving a GnRH agonist who experience convulsion should be managed according to current clinical practice.

5.6 Laboratory Tests

Monitor serum levels of testosterone following injection of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-month administration. In the majority of patients, testosterone levels increased above baseline during the first week, and then declined thereafter to castrate levels (< 50 ng/dL) within four weeks. [*see Clinical Studies (14) and Adverse Reactions (6)*].

5.7 Embryo-Fetal Toxicity

Based on findings in animal studies, LEUPROLIDE ACETATE INJECTION DEPOT may cause fetal harm when administered to a pregnant woman. In animal developmental and reproductive toxicology studies, administration of the monthly formulation of leuprolide

acetate on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose, based on body surface area, using an estimated daily dose. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus [*see Use in Specific Populations (8.1)*].

6. ADVERSE REACTIONS

The following is discussed in more detail in other sections of the labeling:

- Tumor Flare [*see Warnings and Precautions (5.1)*]
- Hyperglycemia and Diabetes [*see Warnings and Precautions (5.2)*]
- Cardiovascular Disease [*see Warnings and Precautions (5.3)*]
- Effect on QT/QTc Interval [*see Warnings and Precautions (5.4)*]
- Convulsions [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-Month Administration

In a clinical trial of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-month administration, patients were treated for 24 weeks with 157/163 receiving two injections. The table includes adverse reactions were reported in 5% or more of the patients during the treatment period as well as the incidence of these adverse reaction that were considered, by the treating physician, to be at least possibly related to LEUPROLIDE ACETATE INJECTION DEPOT. Grade 3-4 adverse reactions reported as treatment-emergent in 13% of patients and treatment-related 4% of patients.

Table 2. Adverse Reactions Reported in \geq 5% of Patients		
LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-Month Administration		
N = 163 (%)		
	Grade 1-4	
	Treatment-Emergent	Treatment-Related
Hot Flush/Flushing*	128 (79)	127 (78)
Upper Respiratory Infection†	28 (17)	0
Fatigue/Asthenia	24 (15)	22 (13)
Diarrhea	21 (13)	2 (1)
Pollakiuria	20 (12)	3 (2)
Arthralgia/Arthritis	18 (11)	2 (1)
Injection Site Pain/Discomfort	18 (11)	15 (9)
Constipation	15 (9)	1 (0.6)
Extremity Pain	14 (9)	0
Nausea	14 (9)	4 (2)
Nocturia	14 (9)	3 (2)
Abdominal Pain/Discomfort	13 (8)	1 (0.6)
Urinary Tract Pain	13 (8)	2 (1)
Dizziness	12 (7)	2 (1)

Headache/Sinus Headache	12 (7)	1 (0.6)
Urinary Tract Infection	12 (7)	0
Bone Pain	11 (7)	4 (2)
Back Pain	10 (6)	1 (0.6)
Hypertension/Blood Pressure Increased	10 (6)	0
Pruritus/Generalized Pruritus	9 (6)	3 (2)

CTCAE v.3

* Includes cold sweat, flushing, hot flush, hyperhidrosis, and night sweats

† Includes influenza, influenza-like illness, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract infection and congestion

In the same study, erectile dysfunction and testicular atrophy were reported in patients on LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg.

Laboratory abnormalities

During the treatment period, at least a one grade change in laboratory values was seen (>10%) in the following: anemia, increased triglyceride, hyperglycemia, increased cholesterol, increased creatine kinase, leukopenia, increased AST, increased creatinine, and increased ALT.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of gonadotropin-releasing hormone agonists. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pituitary apoplexy: During postmarketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH 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 nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Immune Disorders: Anaphylaxis

Psychiatric Disorders: Depression

Respiratory Disorders: Pneumonitis, Interstitial Lung Disease

7. DRUG INTERACTIONS

No pharmacokinetic-based drug-drug interaction studies have been conducted with LEUPROLIDE ACETATE INJECTION DEPOT.

7.1 Drug/Laboratory Test Interactions

Administration of LEUPROLIDE ACETATE INJECTION DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Due to the suppression of the pituitary-gonadal system by LEUPROLIDE ACETATE INJECTION DEPOT, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to three months after discontinuation of LEUPROLIDE ACETATE INJECTION DEPOT may be affected.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings in animal studies and mechanism of action, LEUPROLIDE ACETATE INJECTION DEPOT may cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies, administration of a monthly formulation of leuprolide acetate on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose based on body surface area using an estimated daily dose (*see data*). Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.

Animal Data

Major fetal malformations were observed in developmental and reproductive toxicology studies in rabbits after a single administration of the monthly formulation of leuprolide acetate on day 6 of pregnancy at doses of 0.00024, 0.0024, and 0.024 mg/kg (approximately 1/1600 to 1/16 the human dose based on body surface area using an estimated daily dose in animals and humans). Since a depot formulation was utilized in the study, a sustained exposure to leuprolide was expected throughout the period of organogenesis and to the end of gestation. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of leuprolide acetate in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.2. Lactation

The safety and efficacy of LEUPROLIDE ACETATE INJECTION DEPOT have not been established in females. There is no information regarding the presence of LEUPROLIDE ACETATE INJECTION DEPOT in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in a breastfed child from LEUPROLIDE ACETATE INJECTION DEPOT, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

8.3. Females and Males of Reproductive Potential

Infertility

Males

Based on findings in animals and mechanism of action, LEUPROLIDE ACETATE INJECTION DEPOT may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of LEUPROLIDE ACETATE INJECTION DEPOT in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical trials for LEUPROLIDE ACETATE INJECTION DEPOT in prostate cancer 74% of the patients studied were at least 65 years of age. Hot flushes occurred with equal frequency in those less than or at least 65 years of age.

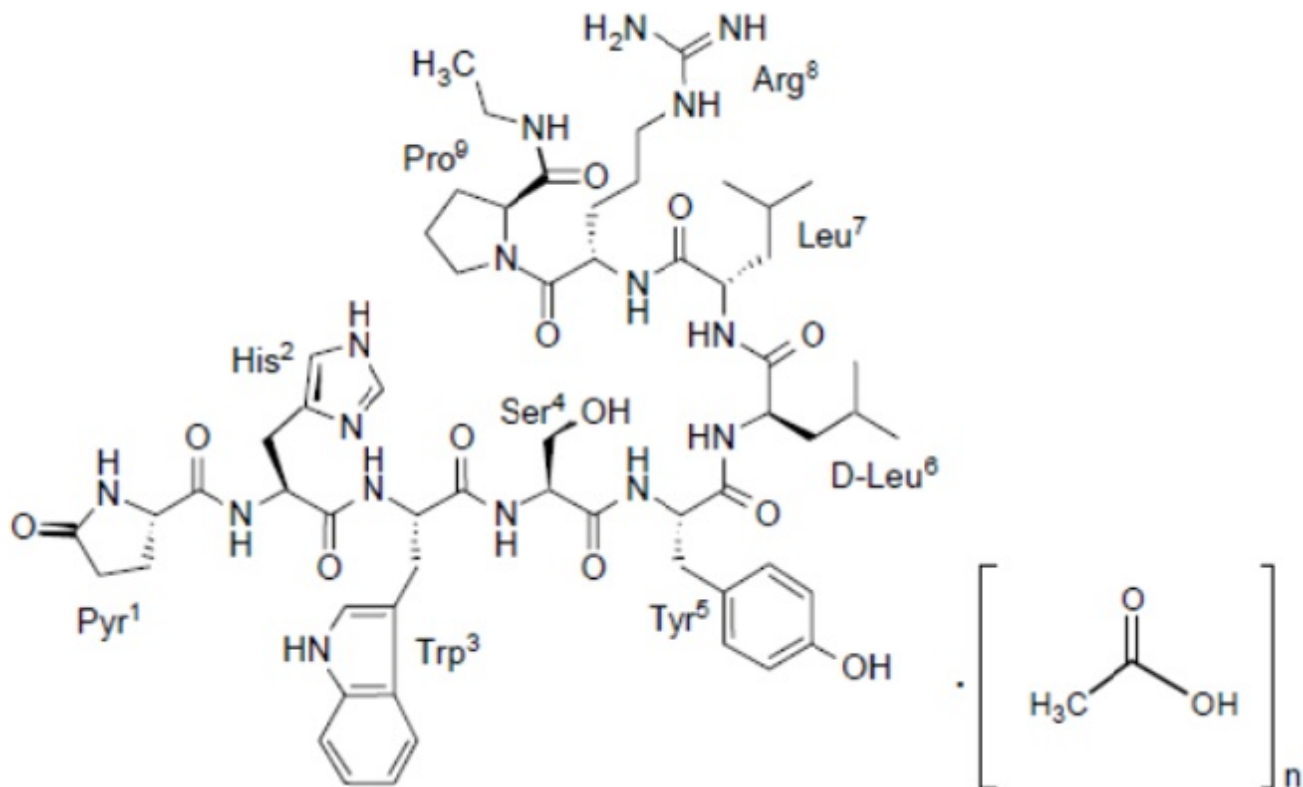
10. OVERDOSAGE

There is no experience of over dosage in clinical trials. In rats, a single subcutaneous dose of 100 mg/kg (approximately 4,000 times the estimated daily human dose based on body surface area), resulted in dyspnea, decreased activity, and excessive scratching.

In early clinical trials with daily subcutaneous leuprolide acetate, 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.

11. DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Where: $n=1$ or 2

Leuprolide acetate has a molecular weight of 1209.41 as free base". Leuprolide is freely soluble in water.

LEUPROLIDE ACETATE INJECTION DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration is available in a vial containing white to off white sterile lyophilized microspheres together with the corresponding sterile reconstitution diluent in a pre-filled syringe. When LEUPROLIDE ACETATE INJECTION DEPOT and the diluent are mixed together they become a suspension intended as an intramuscular injection to be given **ONCE EVERY 12 WEEKS** as a single dose.

Each vial of LEUPROLIDE ACETATE INJECTION DEPOT (leuprolide acetate for depot suspension) 22.5 mg for 3-month administration delivers leuprolide acetate (22.5 mg), polylactic acid (188.4 mg), triethylcitrate (10.4 mg), polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg). The prefilled syringe containing the clear reconstitution diluent (2 mL) contains mannitol (16 mg), water for injections, and sodium hydroxide and hydrochloric acid to control pH.

Leuprolide acetate for depot suspension is an extended release sterile, single dose injection in suspension form for intramuscular administration.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. Animal studies indicate that following an initial stimulation, continuous administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect was reversible upon discontinuation of drug therapy.

Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

12.2 Pharmacodynamics

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold. In premenopausal females, estrogens are reduced to postmenopausal concentrations. These decreases occur within two to four weeks after initiation of treatment. Long-term studies have shown that continuation of therapy with leuprolide acetate maintains testosterone below the castrate level for more than five years.

Leuprolide acetate is not active when given orally.

12.3 Pharmacokinetics

Absorption

Following two sequential injections of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg administered with a 3-month interval, plasma leuprolide concentrations were similar among both cycles. After first administration, mean plasma leuprolide concentration of 46.8 ng/mL was observed at approximately 2 hours and the mean concentration then declined until next injection.

Distribution

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

Elimination

The mean systemic clearance of leuprolide following intravenous bolus administration to healthy male volunteers was 7.6 L/h, and terminal elimination half-life was approximately 3 hours based on a two-compartment model.

Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M- 1) metabolite.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted with leuprolide acetate 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 drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced

tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide 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. No carcinogenicity studies have been conducted with LEUPROLIDE ACETATE INJECTION DEPOT.

Genotoxicity studies were conducted with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of mutagenic effects or chromosomal aberrations.

Leuprolide may reduce male and female fertility. Administration of leuprolide acetate to male and female rats at dose of 0.024, 0.24, and 2.4 mg/kg as monthly depot formulation for up to 3 months (approximately as low as 1/30 of the human dose based on body surface area using an estimated daily dose in animals and humans) caused atrophy of the reproductive organs, and suppression of reproductive function. These changes were reversible upon cessation of treatment.

14 CLINICAL STUDIES

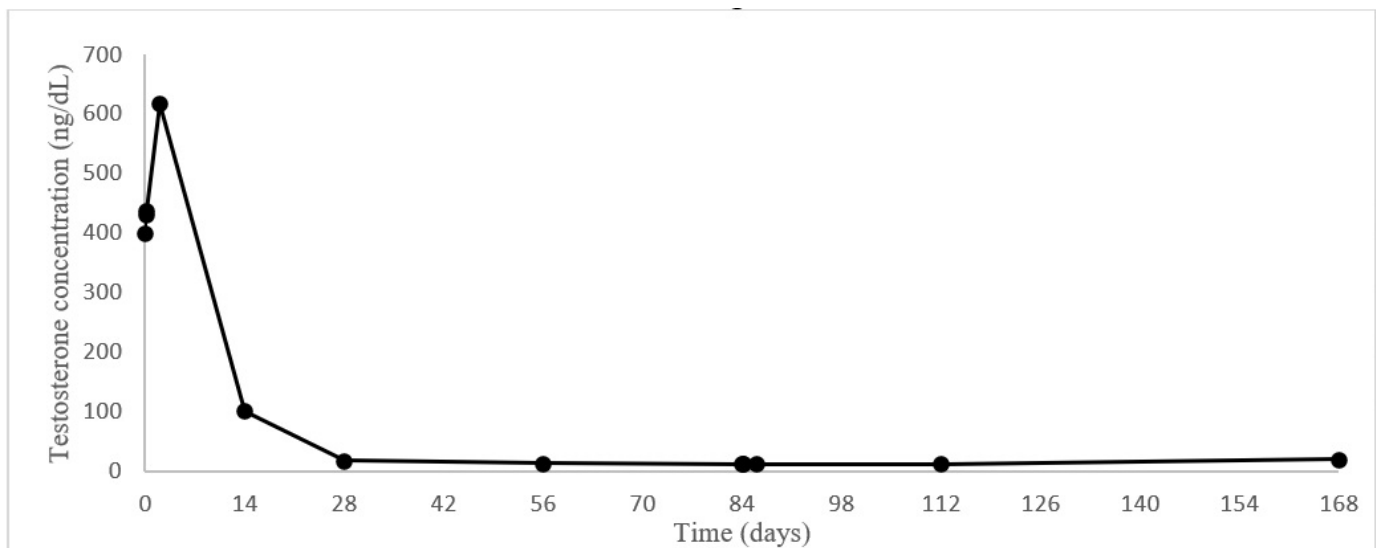
14.1 LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg for 3-Month Administration

The efficacy of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg was evaluated in an open-label, multicenter, non-controlled, multiple dose clinical trial which enrolled 162 evaluable patients with prostate cancer. Patients were administered LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg intramuscularly in 2 doses (157 received 2 injections) with a 3-month interval.

The median age was 71 years (range; 47-91), 62% White, and 30% Black or African-American.

Castrate levels of serum testosterone (<50 ng/dL) were achieved and maintained from Day 28 to 168 in 94.3% (95% CI:89.4, 97.0) of patients. On Day 28, 160 of the 162 (98.8%) patients had castrate testosterone levels. One patient did not achieve a castrate level and one had a missing value. Testosterone escapes (any value > 50 ng/dL after castrate levels were achieved) occurred in four patients. In addition, three patients had a single unevaluable testosterone level after Day 28 that was considered to be non-castrate in this analysis.

Figure 1. Mean testosterone plasma levels during treatment with two three-month IM injections of LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg



15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA.
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

LEUPROLIDE ACETATE INJECTION DEPOT (leuprolide acetate for depot suspension) is supplied as a kit consisting of a LEUPROLIDE ACETATE INJECTION MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile, white to off white lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing clear sterile mannitol solution for injection, USP, 2 mL, pH 4.5 to 7.0.

LEUPROLIDE ACETATE INJECTION DEPOT 22.5 mg - NDC 69097-909-50

Storage

Store at controlled room temperature at 20°-25°C (68°-77°F); excursions permitted between 15°C and 30°C (59°C and 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

- Inform patients that if they have experienced hypersensitivity with other GnRH agonist drugs like LEUPROLIDE ACETATE INJECTION DEPOT, LEUPROLIDE ACETATE INJECTION DEPOT is contraindicated [*see Contraindications (4)*].

Tumor Flare

- Inform patients that LEUPROLIDE ACETATE INJECTION DEPOT can cause tumor flare during the first weeks of treatment. Inform patients that the increase in testosterone can cause an increase in urinary symptoms or pain. Advise patients to contact their healthcare provider if uretral obstruction, spinal cord compression, paralysis, or new or worsened symptoms occur after beginning LEUPROLIDE ACETATE INJECTION DEPOT treatment [*see Warnings and Precautions (5.1)*].

Hyperglycemia and Diabetes

- Advise patients that there is an increased risk of hyperglycemia and diabetes with LEUPROLIDE ACETATE INJECTION DEPOT therapy. Inform patients that periodic monitoring for hyperglycemia and diabetes is required when being treated with LEUPROLIDE ACETATE INJECTION DEPOT [*see Warnings and Precautions (5.2)*].

Cardiovascular Disease

- Inform patients that there is an increased risk of myocardial infarction, sudden cardiac death, and stroke with LEUPROLIDE ACETATE INJECTION DEPOT treatment. Advise patients to immediately report signs and symptoms associated with these events to their healthcare provider for evaluation [*see Warnings and Precautions (5.3)*].

Urogenital Disorders

- Advise patients that LEUPROLIDE ACETATE INJECTION DEPOT may cause impotence.

Infertility

- Inform patients that LEUPROLIDE ACETATE INJECTION DEPOT may cause infertility [*see Use In Specific Populations (8.3)*].

Continuation of LEUPROLIDE ACETATE INJECTION DEPOT Treatment

- Inform patients that LEUPROLIDE ACETATE INJECTION DEPOT is usually continued, often with additional medication, after the development of metastatic castration-resistant prostate cancer [*see Dosage and Administration (2.1)*].

For more information or a video demonstration on how to use, scan the code below or call 1-866-604-3268.



Manufactured by:
GP-PHARM, S.A.
08777 Sant Quintí de Mediona
Spain

Distributed by:
Cipla USA, Inc.
10 Independence Boulevard, Suite 300
Warren, NJ 07059

Rx only

Revised: 05/2022

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LP3M605-US-01

PR-

NDC 69097-909-50

Rx Only

**Leuprolide acetate
for depot suspension**

22.5 mg

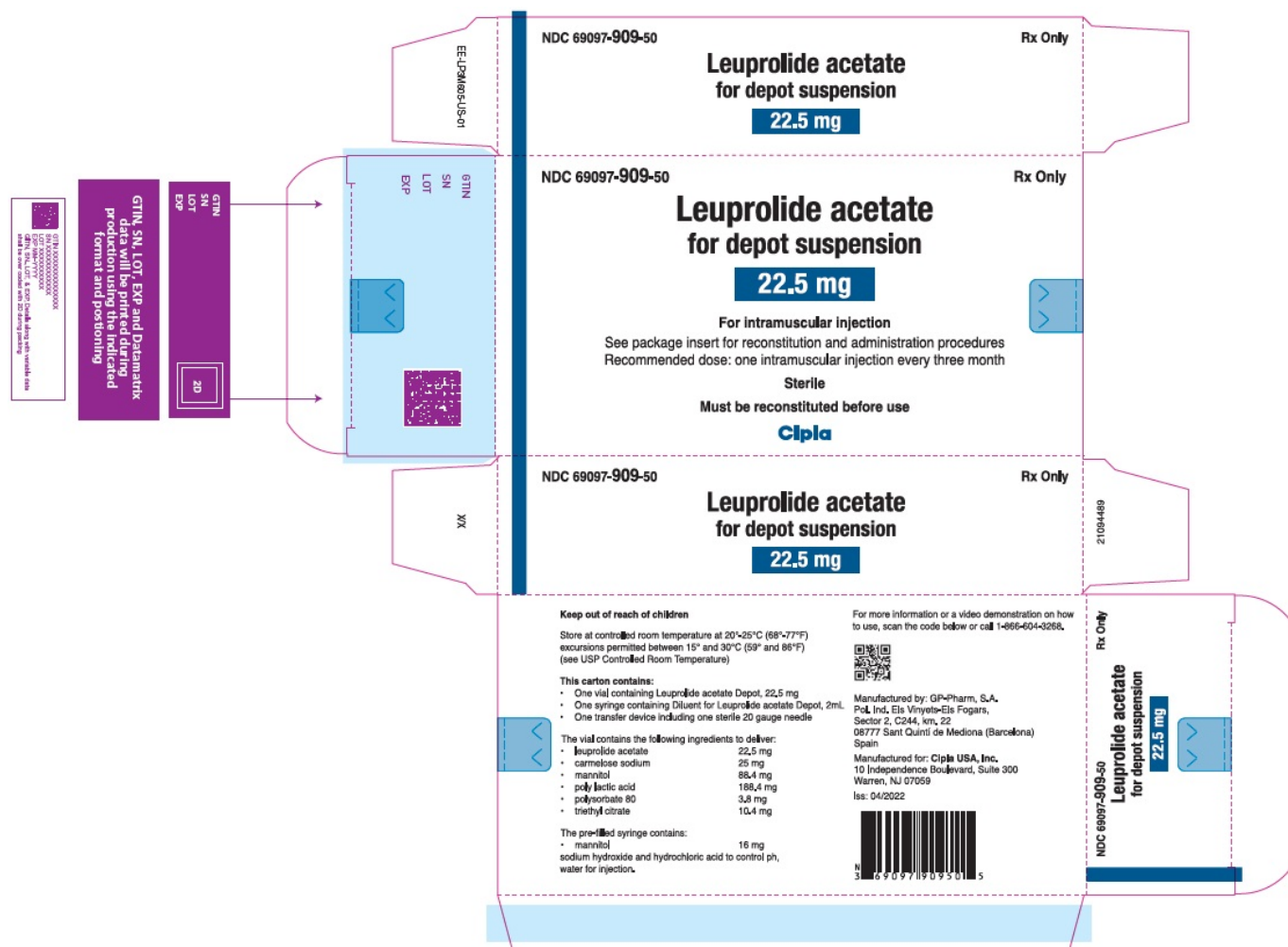
For intramuscular injection

See package insert for reconstitution and administration procedures
Recommended dose: one intramuscular injection every three month

Sterile

Must be reconstituted before use

Cipla



NDC 69097-960-31

Rx Only

2 mL mannitol solution (0.8% w/v)

Diluent

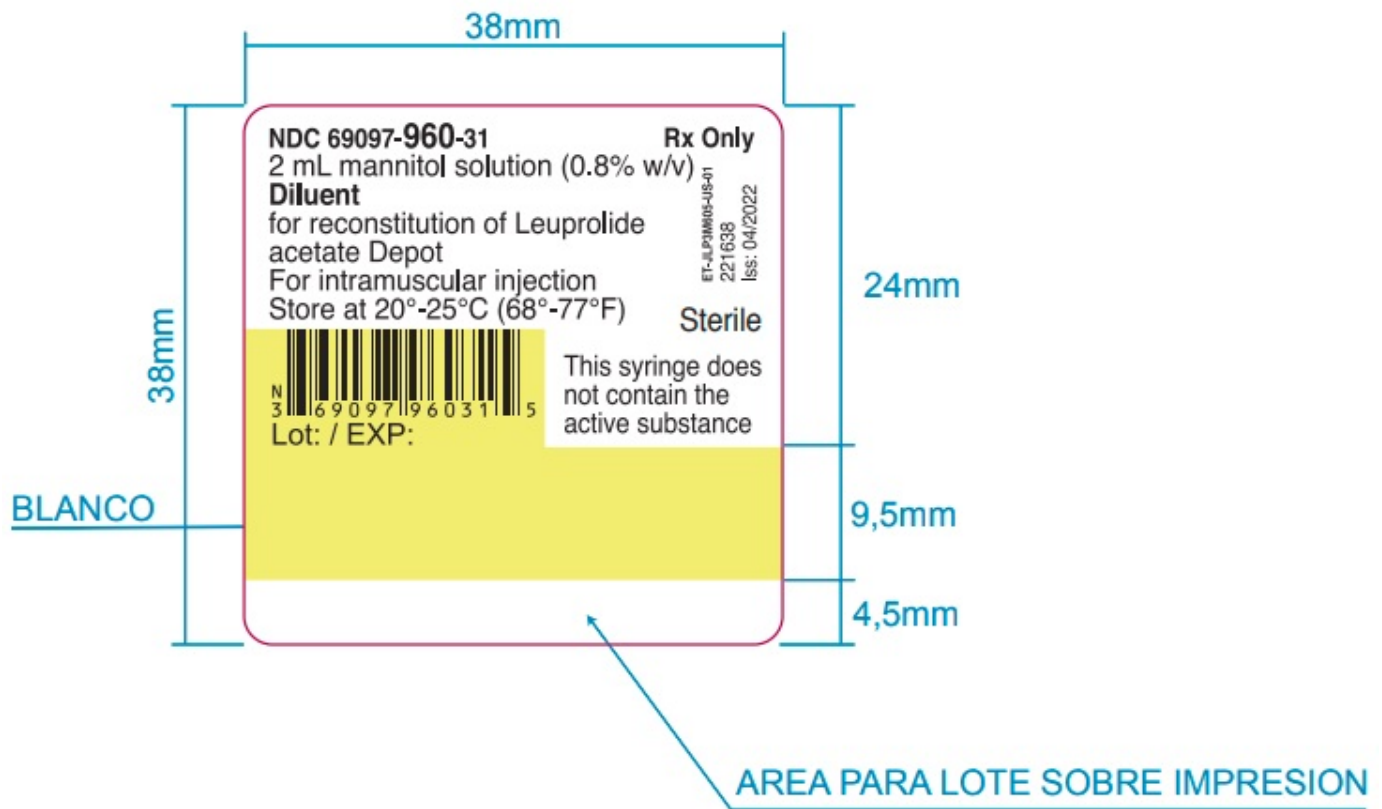
for reconstitution of Leuprolide
acetate Depot

For intramuscular injection

Store at 20°-25°C (68°-77°F)

Sterile

This syringe dose
not contain the
active substance



NDC 69097-950-32

Rx Only

**Leuprolide acetate
for depot suspension**

22.5 mg

Store at 20°-25°C (68°-77°F)

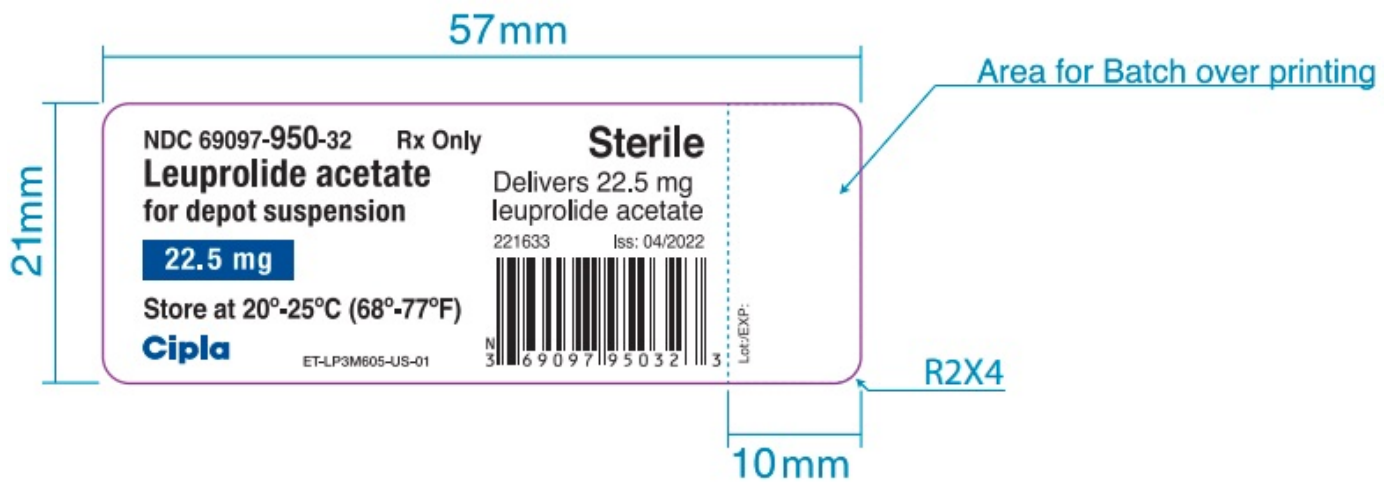
Cipla

Sterile

Delivers 22.5 mg
leuprolide acetate

221633

Iss:04/2022



LEUPROLIDE ACETATE DEPOT

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69097-909
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69097-909-50	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	07/15/2022	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	2 mL
Part 2	1 SYRINGE	2 mL

Part 1 of 2

LEUPROLIDE ACETATE

leuprolide acetate injection, powder, lyophilized, for suspension, extended release

Product Information

Item Code (Source)	NDC:69097-950
Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	22.5 mg in 2 mL
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Inactive Ingredients

Ingredient Name	Strength
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED (UNII: K679OBS311)	25 mg in 2 mL
MANNITOL (UNII: 3OWL53L36A)	88.4 mg in 2 mL
POLYLACTIDE (UNII: 459TN2L5F5)	188.4 mg in 2 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	3.8 mg in 2 mL
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	10.4 mg in 2 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69097-950-32	2 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205054	07/15/2022	

Part 2 of 2

DILUENT

mannitol solution injection

Product Information

Item Code (Source)	NDC:69097-960
Route of Administration	INTRAMUSCULAR

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69097-960-31	2 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205054	07/15/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205054	07/15/2022	

Labeler - CIPLA USA INC. (078719707)

Establishment

Name	Address	ID/FEI	Business Operations
GP PHARM SA		462006581	manufacture(69097-909)

Revised: 7/2022

CIPLA USA INC.