Powerful drug, Designated drug, Prescription drug

Leuplin Depot 3M 11.25 mg S.C. Injection

"TAKEDA"

Leuprolide Acetate for injection

Storage: Store under 25℃.
Expiration date: Do not use after the expiration date indicated on the package.
(Use as soon as possible after unsealing, even before the expiration date.)

CONTRAINDICATIONS Leuplin Depot 3M is contraindicated in the following patients.)

1) Patients with a history of hypersensitivity to any of the ingredients of this drug or synthetic LH-RH or LH-RH derivatives
For Endometriosis and Uterine Leiomyomata (Fibroids)
2) Pregnant women or women having possibilities of being pregnant, or nursing mothers.
3) Patients with abnormal genital bleeding of indeterminable nature [There is a possibility of malignant disease.]
For Premenopausal breast cancer as postoperative supplementary treatment
4) Pregnant women or women having possibilities of being pregnant, or nursing mothers (See PRECAUTIONS 4. Use during Pregnancy, Delivery or Lactation.)
5) In girls with central precocious puberty: pregnancy and lactation; undiagnosed vaginal bleeding

DESCRIPTION

Leuplin Depot 3M is a white powdered lyophilizate.

Active ingredient	Leuprorelin Acetate	11.25 mg
Vehicles	Lactic acid polymer D-mannitol	99.3 mg 19.45 mg

Leuplin Depot 3M is a kit preparation, and consists of powder part and liquid part (1 ml vehicle for suspension). One ml of vehicle for suspension contains water for injection, and 50 mg of D-mannitol, 5 mg of carmellose sodium, and 1 mg of polysorbate 80 as inactive ingredients.
Leuplin Depot 3M when suspended with 1 ml of the attached vehicle for suspension, shows a pH value of 6.0 - 7.1 and an osmotic pressure ratio (relative to isotonic sodium chloride solution) of about 1.

INDICATIONS

Prostate Cancer, Endometriosis, Menorrhagia and anemia cause by uterine fibroids who intends to carry out surgical resection, Premenopausal breast cancer as postoperative supplementary treatment, treatment of central precocious puberty

Prostate Cancer.
Patients with prostate cancer where Leuplin Depot 3M or other medications with similar mechanism has been treated and the serum testosterone concentrations drop to ≤ 50 ng/dl.
Endometriosis
Leuplin Depot 3M is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Leuplin Depot 3M with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 6 months.
Uterine Leiomyomata (Fibroids)
Leuplin Depot 3M concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. (See **Table 1, CLINICAL STUDIES** section.) Leuplin Depot 3M may be added if the response to iron alone is considered inadequate. Recommended therapy is a single injection of Leuplin Depot 3M This dosage form is indicated only for women for whom three months of hormonal suppression is deemed necessary.
Experience with Leuplin Depot 3M in females has been limited to women 18 years of age and older treated for no more than 6 months.
Premenopausal breast cancer as postoperative supplementary treatment:
Patients with pre- and perimenopausal endocrine-responsive (ER-/PgR-positive) breast cancer where an endocrine treatment is indicated

<Precautions for INDICATIONS>
Uterine Leiomyomata (Fibroids)
It should be noted that the treatment of uterine myoma with Leuplin Depot 3M is not a radical treatment. Therefore, as a rule, this drug should be used as a means of providing conservative treatment until operation on patients requiring operation or providing premenopausal conservative treatment. For hypogastralgia and low back pain, the effect of this drug is not observed at the early period after administration. During such a period, therefore, appropriate symptomatic treatment should be given.

DOSAGE AND ADMINISTRATION

Use only pursuant to the prescription of a physician.
Usually, for adults, 11.25 mg of Leuprorelin Acetate is subcutaneously administered once every 12 weeks.
When using Leuplin Depot 3M, it should be used after suspending it completely by transferring the whole quantity of the vehicle into the powder part, by pressing the plunger rod, with the injection needle held upward, with caution against foaming.
Prostate Cancer
When 11.25mg mg of Leuprorelin Acetate is used in patients with prostate cancer, a periodic monitoring of serum testosterone concentration, at least once per three months, within 6 months treatment is required.
Endometriosis
The recommended duration of treatment with Leuplin Depot 3M alone or in combination with norethindrone acetate is six months. The choice of Leuplin Depot 3M alone or Leuplin Depot 3M 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 Leuplin Depot 3M alone.
If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of Leuplin Depot 3M 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. Leuplin Depot 3M 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 and management of risk factors such as cigarette smoking is recommended before beginning treatment with Leuplin Depot 3M and norethindrone acetate.
Uterine Leiomyomata (Fibroids)
The recommended dose of Leuplin Depot 3M is one injection. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy.

If additional treatment with Leuplin Depot 3M is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

Central Precocious Puberty:

The treatment of children with leuprorelin acetate should be under the overall supervision of the pediatric endocrinologist.
The dosing scheme needs to be adapted individually.
The recommended starting dose is dependent on the body weight.

Children with a body weight ≥ 20 kg:
1 ml (11.25 mg leuprorelin acetate) suspension of 130.0 mg sustained-release microcapsules in 1 ml vehicle solution are administered every 3 months as a single subcutaneous injection.

Children with a body weight < 20 kg:
In these rare cases, the following dosage should be administered according to the clinical activity of the central precocious puberty:
0.5 ml (5.625 mg leuprorelin acetate) suspension of 130.0 mg sustained-release microcapsules in 1 ml vehicle solution are administered every 3 months 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). The minimal effective 3-monthly dose to be administered should then be determined by means of the LHRH test.
Sterile abscesses at the injection site often occurred when leuprorelin acetate was administered intramuscularly at higher than the recommended dosages. Therefore, in such cases, the medicinal product should be administered subcutaneously.
It is recommended to use the lowest volumes possible for injections in children in order to decrease the inconvenience which is associated with the intramuscular/subcutaneous 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 pediatrician together with the legal guardian and, if appropriate, the treated child. The bone age should be monitored during treatment at 6-12 month intervals.
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.
In girls, pregnancy should be excluded before the start of treatment. The occurrence of pregnancy during treatment cannot be generally excluded. In such cases, medical advice should be sought.
Note:
The administration interval should be 90 ± 2 days in order to prevent the recurrence of precocious puberty symptoms.

< PRECAUTIONS FOR DOSAGE AND ADMINISTRATION>

For treatment of all indications

Since Leuplin Depot 3M is a sustained release preparation with its action lasting 12 weeks, administration at an interval exceeding 12 weeks may lead to the recurrence of an increase in the serum level of testosterone due to the pituitary-gonad system stimulating effect of this drug, resulting in a transient aggravation of the clinical condition. Therefore, the method of administering once every 12 weeks should be observed.
Hyperglycemia and Diabetes: it has been reported that GnRH agonist may increase the risk of hyperglycemia occurrence or develop of diabetes on male patient. Therefore, it should follow the currently clinical routine to monitor and control patients' blood glucose.
Cardiovascular disease: it has been reported that GnRH agonist may increase the risk of cardiac arrest, stroke and myocardial infarction on male patient. Therefore, it should follow the currently clinical routine to monitor and control the occurrence of cardiovascular diseases

Endometriosis and Uterine Leiomyomata (Fibroids)

(1) The incidence of adverse reactions generally tends to increase with an increase in dose. Thus, in setting the dose, careful attention should be paid to the body weight and the extent of enlargement of the uterus shown in Dosage and Administration.
(2) Before starting treatment with Leuplin Depot 3M , confirmation should be made that the patient is not pregnant. It is imperative the administration is initiated on the first to fifth day after the start of menstrual period. During the period of treatment with Leuplin Depot 3M , the patient should be instructed to prevent conception with the use of a non-hormonal method.
(3) A decrease in bone mass may occur owing to estrogen reducing effect of Leuplin Depot 3M . Therefore, as a rule, this drug should not be administered to patients with endometriosis or uterine myoma for more than 6 months. (The safety of administration for more than 6 months has not been established.) The induced hypoestrogenic state also results in a loss in bone density over the course of treatment, some of which may not be reversible. For a period up to six months, this bone loss should not be clinically significant. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with Leuplin Depot 3M. (All patients received calcium supplementation with 1000 mg elemental calcium.)

In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with Leuplin Depot 3M alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including Leuplin Depot 3M is not advisable in patients with major risk factors for loss of bone mineral content.

When it is inevitable to administer this drug for a long period or to resume its administration, the drug should be carefully administered after the bone mass is examined as far as possible.

Premenopausal breast cancer

(1) Before starting treatment, it should be confirmed that the patient is not pregnant. During the period of treatment with Leuplin Depot 3M, the patient should be instructed to prevent conception with the use of a non-hormonal method.
(2) A decrease in bone mass may occur owing to estrogen reducing effect of Leuplin Depot 3M. Therefore, when this drug is administered for a long period, the drug should be carefully administered after bone mass is examined as far as possible.

PRECAUTIONS

1. **Careful Administration** (Leuplin Depot 3M should be administered with care in the following patients.)

   For treatment of Prostate cancer

   Patients who have already had renal dysfunction due to spinal cord compression or ureteral obstruction or those who may be at a risk of developing such manifestations. [There is a possibility that the symptoms of underlying disease are aggravated with the elevation of serum testosterone level in the early period after the first administration.]

   For treatment of Endometriosis and Uterine Leiomyomata (Fibroids)

   Patients with submucous myoma [Bleeding symptom may be aggravated.] (See 2. Important Precautions.)

   For Treatment of Premenopausal breast cancer

   Patients with submucous myoma (Bleeding symptom may be aggravated)

2. **Important Precautions**

   For treatment of Prostate cancer

   (1) Since Leuplin Depot 3M is an agent for endocrine therapy, use of this drug for prostate cancer should be limited to patients for whom treatment with Leuplin Depot 3M is considered appropriate under the supervision of a physician who has adequate knowledge and experience in medication for cancer.
   (2) Since Leuplin Depot 3M is a long-acting preparation with its action lasting 12 weeks, this sustained release drug may stay at the injection site for a long time, resulting in formation of induration. Therefore, Leuplin Depot 3M should be administered with extreme caution such as to change the injection site

each time and to instruct the patient not to massage the injection site (See 3. Adverse Reactions and 5. Precautions concerning Use).

(3) In the early period after the first administration of Leuplin Depot 3M, a transient elevation of the serum level of testosterone may occur owing to the stimulating effect of Leuplin Depot 3M, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of bone pain, etc. In such a case, symptomatic treatment should be given. Since ureteral obstruction or spinal cord compression may occur, this drug should be carefully administered and close observation should be made during the first month after initiation of administration, and if any of such symptoms occurs, appropriate measures should be taken.

(4) 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.

For treatment of endometriosis

(1) In administration of Leuplin Depot 3M, care should be taken to differentiate a similar disease (malignant tumor, etc.) from endometriosis. If, during administration of Leuplin Depot 3M, any growing phyma is found or no improvement is seen in the clinical symptom, the administration should be discontinued.

(2) In the early period after the first administration of Leuplin Depot 3M, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of Leuplin Depot 3M, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of clinical condition. However, such an aggravation usually disappears in the course of continued administration.

(3) Since a depressed state like climacteric disturbance may occur, the patient's condition should be closely observed. (See 4. (1) Clinically significant adverse reactions)

For treatment of Uterine Leiomyomata (Fibroids)

(1) In administration of Leuplin Depot 3M, care should be taken to differentiate a similar disease (malignant tumor, etc.) from uterine myoma. If, during administration of Leuplin Depot 3M, any growing phyma is found or no improvement is seen in the clinical symptom, the administration should be discontinued.

(2) In administration of Leuplin Depot 3M to patients with submucous myoma, bleeding symptom may worsen. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures should be taken. In addition, the patients should be instructed to contact the attending physician in case of any aggravation of the bleeding symptom.

(3) In the early period after the first administration of Leuplin Depot 3M, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of LEUPLIN®, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of clinical condition. However, such an aggravation usually disappears in the course of continued administration.

(4) Since a depressed state like climacteric disturbance may occur, the patient's condition should be closely observed. (See 4. (1) Clinically significant adverse reactions.)

For treatment of premenopausal breast cancer

(1) In the early period after the first administration of Leuplin Depot 3M, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of Leuplin Depot 3M, as a highly active LH-RH derivative, on the pituitary-gonad system, resulting in a transient aggravation of bone pain, etc. In such a case, symptomatic treatment should be given.

(2) If antitumor effect is not obtained with Leuplin Depot 3M and any progression of the tumor is observed, the administration should be discontinued.

(3) Since a depressed state like climacteric disturbance may occur, the patient's condition should be closely observed. (See 3. (1) Clinically significant adverse reactions.)

For Central Precocious Puberty:

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

The therapy is a long-term treatment, adjusted individually. Leuplin Depot 3M should be administered as precisely as possible in regular 3-monthly periods. An exceptional delay of the injection date for a few days (90 + 2 days) does not influence the results of the therapy.

In the event of a sterile abscess at the injection site (mostly reported after i.m. injection of higher than the recommended dosage) the absorption of leuprorelin acetate from the depot can be decreased. In this case the hormonal parameters (testosterone, estradiol) should be monitored at 2-week intervals.

The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

The occurrence of vaginal bleeding, spotting and discharge after the first injection may occur as a sign of hormone withdrawal in girls. Vaginal bleeding beyond the first/second month of treatment needs to be investigated.

Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved, and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

3. Drug Interactions

Endometriosis, Uterine Leiomyomata (Fibroids)

Precautions for coadministration (LEUPLIN® should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanisms and Risk Factors
Sex hormone preparations Estradiol derivatives, Estriol derivatives, Conjugated estrogen preparations, Combined preparations of estrogen and progesteron, Mixed sex hormones, etc.	The effects of LEUPLIN® may be reduced.	LEUPLIN® exerts its therapeutic effects by reducing the secretion of sex hormones. Consequently, administration of sex hormones may reduce the therapeutic effect of this product.

4. Adverse Reactions

(1) Clinically significant adverse reactions

For treatment of all indications

1) Since interstitial pneumonia, accompanied by fever coughing, dyspnea, abnormal chest X-ray, etc. may occur (< 0.1%), the patient's condition should be closely observed. If any abnormality is observed, appropriate measures, such as treatment with adrenal cortical hormones, should be taken.

2) Since anaphylactoid symptoms may occur (< 0.1%), careful inquiry should be made, and close observation should be made after the administration of Leuplin Depot 3M. If any abnormality is observed, appropriate measures should be taken.

3) Hepatic dysfunction or jaundice, with increased AST(GOT), ALT(GPT) etc., may occur (frequency unknown). Therefore, close observation should be made, and if any abnormality is observed, appropriate measures should be taken.

4) Development or aggravation of diabetes may occur (frequency unknown). If any abnormality is observed, appropriate measures should be taken.

5) Pituitary apoplexy has been reported in patients with pituitary adenoma (frequency unknown). Therefore, if headache, visual/visual field disorders, etc. are observed immediately after the first dose of LEUPLIN®, appropriate measures, such as surgical treatment, should be taken after conducting examination.

6) Thromboembolic event, such as myocardial infarction, cerebral infarction, venous thrombosis, pulmonary embolism, may occur (frequency unknown). Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of administration, should be taken.

For treatment of Prostate cancer

1) Since a depressed state occur (< 0.1%), the patient's condition should be closely observed.
2) Elevation of serum testosterone level due to the stimulating effect of LEUPLIN on the pituitary-gonad system may bring about a transient aggravation of bone pain, ureteral obstruction or spinal cord compression (≥ 5%). If any of such symptoms occurs, appropriate measures, such as pertinent symptomatic treatment, should be taken
3) Since cardiac failure may occur (0.1- <5%), close observation should be made. If any abnormality is observed, appropriate measures, such as discontinuation of administration, should be taken.

For treatment of Endometriosis and Uterine Leiomyomata (Fibroids)

Since a depressed state like climacteric disturbance resulting from estrogen reducing effect of LEUPLIN® may occur (0.1% -< 5%), the patient's condition should be closely observed.

For Treatment of Premenopausal breast cancer

Since a depressed state like climacteric disturbance resulting from estrogen reducing effect of LEUPLIN® may occur (0.1% - < 5%), the patient's condition should be closely observed.

For treatment of Central precocious puberty:

In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.
Immune system disorders:
Very rare: general allergic reactions (fever, rash, e.g. itching, anaphylactic reactions)
Psychiatric disorders:
Common: emotional lability
Nervous system disorders:
Common: headache
As with other medicinal products of this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.
Gastrointestinal disorders:
Common: abdominal pain / abdominal cramps, nausea/vomiting
Skin and subcutaneous tissue disorders:
Common: acne
Reproductive system and breast disorders:
Common: vaginal bleeding, spotting, discharge
Note:
In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. The pituitary suppression should then be determined by an LHRH test.
General disorders and administration site conditions:
Common: injection site reactions

(2) Other adverse reactions

For treatment of prostate cancer

Adverse reactions, including abnormalities in laboratory data, were observed in 17 (27.9%) of 61 patients that were evaluated for the safety in the clinical studies conducted in Japan. Major adverse reactions are diaphoresis/hidrosis in 3 patients, hot flushes in 2 patients, dermatological disorders (eruption, eczema, rash, dermatitis in 1 patient each), disorder in the administration site (induration and painful induration in the administration site in 1 patient each), decreased RBC, Hb and Ht in 2 patients, increased ALP in 3 patients and increased LDH in 2 patients, etc.
Adverse reactions, including abnormalities in laboratory data, were observed in 144 (66.1%) of 218 patients that were evaluated for the safety in the clinical studies conducted abroad.
Major adverse reactions are hot flushes in 85 patients, hidrosis in 61 patients, decreased libido in 36 patients, erectile dysfunction in 33 patients and weight increase in 33 patients, etc.
During post-marketing 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.

Table 1: Other adverse reactions

	≧5%	0.1% - < 5%	< 0.1%
1) Hepatic	Increased LDH	Jaundice, or increased AST(GOT), ALT(GPT), γ- GTP or ALP	
2) Endocrine	Hot flashes, feeling of warmth	Headache, facial hot flushes, dizziness, diaphoresis, decreased libido, erectile dysfunction, gyecomastia, testicular atrophy or discomfort in the perineal region	
3) Musculo-skeletal		Arthralgia, bone pain, pain in the shoulder, low back or limbs, or difficulty in walking	Muscle ache or decreased bone mass
4) Dermatologic		Dermatitis, or hair growth on the head	
5) Urinary		Pollakiuria, hematuria or increased BUN	
6) Cardiovascular		ECG abnormalities or increased cardiothoracic ratio	
7) Hematologic		Anemia or platelet count decreased	
8) Gastrointestinal		Nausea, vomiting or anorexia	Diarrhea
9) Hypersensitivity		Rash or pruritus	
10) Administration site Note1)		Reactions at the injection site, such as pain, induration and redness	Abscess
11) Others		Edema, pressure sensation of chest, rigor, malaise, numbness of lips or limbs, weight increase, paresthesia, deafness, tinnitus, fever, increased total cholesterol, triglyceride or uric acid, hyperkalemia, or increased blood sugar level	Weakness

Note 1) Close observation should be made

For treatment of endometriosis and Uterine Leiomyomata (Fibroids)

Table 2 : Other adverse reactions (observed in Leuplin Depo 1M)

	≧5%	0.1% - < 5%	< 0.1%
1)Symptoms resulting from decreased estrogen	Hot flushes, feeling of warmth, feeling of hot	Decreased libido, coldness, visual disturbance or emotional lability.	

	flushes, shoulder stiffness, headache, insomnia, dizziness or diaphoresis		
2)Female reproductive		Metrorrhagia, vaginal dryness, coital pain, vaginitis, increased fluor, ovarian hyperstimulation syndrome, or pain, swelling or atrophy of the breast	
3) Musculo-skeletal	Pains, such as arthralgia and bone pain	Joint stiffness, lumbar pain, muscle ache, muscular spasm, decreased bone mass, increased serum phosphorus or hypercalcemia	
4) Dermatologic		Acne, dry skin, alopecia, hypertrichosis or nail abnormality	
5) Psychoneurologic		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia	
6) Hypersensitivity		Rash or pruritus	
7)Hepatic[Note 1)]		Increased AST(GOT), ALT(GPT), ALP, LDH, g-GTP or bilirubin	Jaundice
8) Gastrointestinal		Nausea, vomiting, anorexia, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, stomatitis or thirst	
9) Cardiovascular		Palpitation or increased blood pressure	
10) Hematologic		Red blood cell count increased, anemia, white blood cell decreased, platelet count decreased or prolonged partial thromboplastin time	
11) Urinary		Pollakiuria, dysuria or increased BUN	
12) Administration site		Reactions at the injection site, such as pain, induration and redness	Abscess
13) Others		Fatigue, malaise, weakness, numbness of lips or limbs, carpal tunnel syndrome, tinnitus, deafness, chest discomfort, edema, weight increase, pain of lower extremities, respiratory distress, fever, increased total cholesterol, LDL cholesterol or triglyceride, or hyperkalemia	Weight decrease, taste abnor-mality or abnormal thyroid function

Note 1) Close observation should be made.

For Treatment of Premenopausal breast cancer

Adverse reactions, including abnormalities in laboratory data, were observed in 90 (96.8%) of 93 patients that were evaluated for the safety in the clinical studies conducted in Japan. As for the subjective and objective adverse reactions, symptoms resulting from decreased estrogen, disorder in the administration site, etc. were mainly investigated. Major adverse reactions are feeling of warmth/ hot flashes /feeling of hot flashes/ in 72 patients, headache/dull headache in 45 patients, diaphoresis/night sweats in 18 patients, disorder in the administration site in 42 patients (mainly mild induration), and nausea/vomiting in 21 patients. Administration of Leuplin Depot 3M was discontinued because of feeling of warmth/dull headache/nausea in 1 patient and because of administration site induration/pain in 1 patient.

Also major abnormalities in laboratory data were increased γ-GTP in 16 patients, increased ALT (GPT) in 14 patients, increased AST (GOT) in 11 patients, etc.

Adverse reactions, including abnormalities in laboratory data, were observed in 280 (95.2%) of 294 patients that were evaluated for the safety in the clinical studies conducted abroad. Major adverse reactions are hot flushes in 245 patients, weight increase in 234 patients, excessive sweating in 228 patients, etc.

From the post marketing safety report, adverse reactions including abnormalities in laboratory data, were reported in 121 (19.1%) of 635 patients. The major reported adverse reaction are disorder in the administration site (induration in 40 patients, pain in 17 patients, reddish in 15 patients, swelling in 10 patents), and hot flash in 35 patients.

The following adverse reactions were observed in the above clinical studies, spontaneous reports, etc., or in the clinical studies/investigation, spontaneous reports, etc. of a 4-week sustained release preparation.

Since LEUPLIN DEPOT 3Mis a sustained release preparation, the patient's condition should be observed while the effect of this drug lasts after the final dosing.

Table 3 : Other adverse reactions

	> 5%	0.1% - < 5%	< 0.1%
1) Symptoms resulting from decreased estrogen	Hot flushes, feeling of warmth, feeling of hot flushes, shoulder stiffness, headache, insomnia, dizziness or diaphoresis	Decreased libido, coldness, visual disturbance or emotional lability	
2) Female reproductive		Metrorrhagia, vaginal dryness, coital pain, vaginitis, increased fluor, ovarian hyperstimulation syndrome, or pain, swelling or atrophy of the breast	
3) Musculo-skeletal	Pains, such as arthralgia and bone pain	Joint stiffness, lumbar pain, muscle ache, muscular spasm, decreased bone mass, increased serum phosphorus or hypercalcemia	
4) Dermatologic		Acne, dry skin, alopecia, hypertrichosis or nail abnormality	
5) Psychoneurologic		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia	
6) Hypersensitivity		Rash or pruritus	
7) Hepatic[Note 3)]		Increased AST(GOT), ALT(GPT), ALP, LDH, γ-GTP or bilirubin	Jaundice
8) Gastrointestinal		Nausea, vomiting, anorexia, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, stomatitis or thirst	
9) Cardiovascular		Palpitation or increased blood pressure	
10) Hematologic		Red blood cell count increased, anemia, white blood cell decreased, platelet count decreased or prolonged partial thromboplastin time	
11) Urinary		Pollakiuria, dysuria or increased BUN	

12) Administration site Note 3)	Induration	Reactions at the injection site, such as pain, induration and redness	Abscess
13) Others		Fatigue, malaise, weakness, numbness of lips or limbs, carpal tunnel syndrome, tinnitus, deafness, chest discomfort, edema, weight increase, pain of lower extremities, respiratory distress, fever, increased total cholesterol, LDL cholesterol or triglyceride, or hyperkalemia	Weight decrease, taste abnormality or abnormal thyroid function

Note [3]) Close observation should be made

Clinical Trials in foreign country

The monthly formulation of LEUPLIN DEPOT 3.75 mg was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in ≥ 5% of patients in either of these populations and thought to be potentially related to drug are noted in the following table 3.

Table 4 ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN ≥ 5% OF PATIENTS

	Endometriosis (2 Studies)						Uterine Fibroids (4 Studies)			
	LUPRON DEPOT 3.75 mg N=166		Danazol N=136		Placebo N=31		LUPRON DEPOT 3.75 mg N=166		Placebo N=163	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body as a Whole										
Asthenia	5	(3)	9	(7)	0	(0)	14	(8.4)	8	(4.9)
General pain	31	(19)	22	(16)	1	(3)	14	(8.4)	10	(6.1)
[illegible]	[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	(17.8)

Table 4: TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥ 5% OF PATIENTS

	Controlled Study				Open Label Study	
	LD - Only* N=51		LD/N† N=55		LD/N† N=136	
Adverse Events	N	(%)	N	(%)	N	(%)
Any Adverse Event	50	(98)	53	(96)	126	(93)
Body as a Whole						
Asthenia	9	(18)	10	(18)	15	(11)
Headache/Migraine	33	(65)	28	(51)	63	(46)
Injection Site Reaction	1	(2)	5	(9)	4	(3)
Pain	12	(24)	16	(29)	29	(21)
Cardiovascular System						
Hot flashes/Sweats	50	(98)	48	(87)	78	(57)
Digestive System						
Altered Bowel Function	7	(14)	8	(15)	14	(10)
Changes in Appetite	2	(4)	0	(0)	8	(6)
GI Disturbance	2	(4)	4	(7)	6	(4)
Nausea/Vomiting	13	(25)	16	(29)	17	(13)
Metabolic and Nutritional Disorders						
Edema	0	(0)	5	(9)	9	(7)
Weight Changes	6	(12)	7	(13)	6	(4)
Nervous System						
Anxiety	3	(6)	0	(0)	11	(8)
Depression/Emotional Lability	16	(31)	15	(27)	46	(34)
Dizziness/Vertigo	8	(16)	6	(11)	10	(7)
Insomnia/Sleep Disorder	16	(31)	7	(13)	20	(15)
Libido Changes	5	(10)	2	(4)	10	(7)
Memory Disorder	3	(6)	1	(2)	6	(4)
Nervousness	4	(8)	2	(4)	15	(11)
Neuromuscular Disorder	1	(2)	5	(9)	4	(3)
Skin and Appendages						
Alopecia	0	(0)	5	(9)	4	(3)
Androgen-Like Effects	2	(4)	3	(5)	24	(18)
Skin/Mucous Membrane Reaction	2	(4)	5	(9)	15	(11)
Urogenital System						
Breast Changes/Pain/Tenderness	3	(6)	7	(13)	11	(8)
Menstrual Disorders	1	(2)	0	(0)	7	(5)
Vaginitis	10	(20)	8	(15)	11	(8)

* LD-Only = LUPRON DEPOT 3.75 mg

† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg

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In the controlled clinical trial, 50 of 51 (98%) patients in the LD group (monthly LEUPLIN DEPOT 3.75 mg) and 48 of 55 (87%) patients in the LD/N group (monthly LEUPLIN DEPOT 3.75 mg plus norethindrone acetate 5 mg daily) reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes.

Table 5: MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change	N	Change	N	Change
Week 24*	41	-3.2%	42	-0.3%	115	-0.2%
Week 52†	29	-6.3%	32	-1.0%	84	-1.1%

* Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.

† Includes on-treatment measurements >252 days after the first day of treatment.

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In the Phase IV, six-month pharmacokinetic/pharmacodynamic study in endometriosis patients who were treated with monthly LEUPLIN DEPOT 3.75 mg or LEUPLIN DEPOT 3M, vertebral bone density measured by DEXA decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.

When monthly LEUPLIN DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LEUPLIN® for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss and is not recommended.

Changes in Laboratory Values During Treatment

Liver Enzymes

Three percent of uterine fibroid patients treated with monthly LEUPLIN DEPOT 3.75 mg, manifested posttreatment transaminase values that were at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

In two other clinical trials, 6 of 191 patients receiving monthly LEUPLIN DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Five of the 6 increases were observed beyond 6 months of treatment. None were associated with an elevated bilirubin concentration.

Lipids

Triglycerides were increased above the upper limit of normal in 12% of the endometriosis patients who received monthly LEUPLIN DEPOT 3.75 mg and in 32% of the subjects receiving LEUPLIN DEPOT 3M.

Of those endometriosis and uterine fibroid patients whose pretreatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in endometriosis patients and +11 mg/dL to +29 mg/dL in uterine fibroid patients. In the endometriosis treated patients, increases from the pretreatment values were statistically significant ($p<0.03$). There was essentially no increase in the LDL/HDL ratio in patients from either population receiving monthly LEUPLIN DEPOT 3.75 mg.

In two other clinical trials, monthly LEUPLIN DEPOT 3.75 mg plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. monthly LEUPLIN DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables 6. below.

Table 6. SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0†	5.0%	2.1†	43.4%	2.3†	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%

* mg/dL

† ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data (Table 7) returned to pretreatment values.

Table 7. PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%

* Includes all patients regardless of baseline value.

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 LEUPLIN and norethindrone acetate.

Chemistry

Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant. In the hormonal add-back studies LEUPLIN DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT in 6% to 7% of patients.

5. Use during Pregnancy, Delivery or Lactation

For treatment of Endometriosis, Uterine Leiomyomata (Fibroids) and Premenopausal breast cancer

LEUPLIN® should not be administered to pregnant women, women having possibilities of being pregnant, or nursing mothers. [Abortion due to LH-RH derivatives has been reported. In animal studies of this drug, increased fetal death rate and low fetal body weight were observed (in rats and rabbits), and an increasing tendency for abnormal formation of fetal skeleton was observed (in rabbits). The transfer of leuprorelin acetate to mother's milk was also observed in rats.]
For the indication Central Precocious Puberty, see section Contraindication.

6. Precautions concerning Use

(1) Route of administration

Leuplin Depot 3M should be used only by the subcutaneous route.

[Intravenous injection of Leuplin Depot 3M may induce thrombosis.]

(2) Method of administration

For subcutaneous injection, the following cautions should be exercised.

- The site for subcutaneous injection should be the brachial, abdominal or gluteal region.
- The injection site should be changed each time. The repeated injection should not be given at the same site.
- The check should be made to see that the needle is not piecing a blood vessel.
- The patients should be instructed not to massage the injection site.

(3) Preparation

The injectable solution should be prepared at the time of use and be used immediately after suspending.

7. Other Precautions

For treatment of all indications

It has been reported that the benign pituitary adenoma was observed in rats in a study in which this drug was administered subcutaneously in doses of 0.8, 3.6 and 16 mg (as leuprorelin acetate)/kg at 4-week intervals for 1 year and another study in which an aqueous injectable solution of Leuprorelin Acetate was similarly administered in doses of 0.6, 1.5 and 4 mg/kg/day for 2 years.

For treatment of Prostate cancer

It has been reported that cerebral infarction, venous thrombosis, pulmonary embolism may occur after administered.

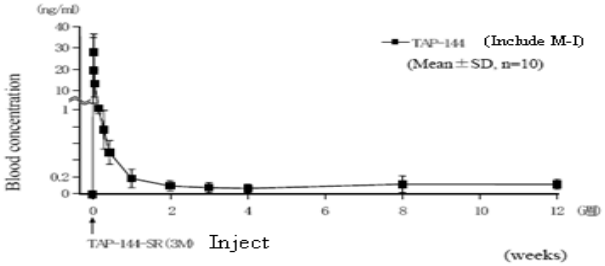
For treatment of Premenopausal breast cancer

It has been reported that the administration of Leuprorelin Acetate brought about venous thrombosis or pulmonary embolism.

PHARMACOKINETICS

The blood concentration after single dose Leuprorelin Acetate 11.25mg administered subcutaneously to prostate cancer patient(untreated patient)(the unchanged compound and its metabolite M-I) as below:

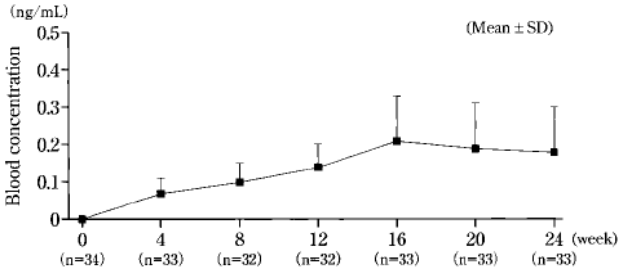
*M-1: Try-D-Leu-Leu-Arg-Pro-NH_2CH_5



The blood concentration (the unchanged compound and its metabolite M-I) observed after subcutaneous administration 2 times with an interval of 12 weeks at 11.25 mg as Leuprorelin Acetate to 51 treated prostate cancer patients, that stable antitumor effect has obtained by the subcutaneous administration at 3.75 mg as leuprorelin acetate, fluctuated mostly at 0.2 - 0.3 ng/mL until 24 weeks after administration. In view of the changes in blood concentration, there seemed to be no accumulation of drug.

Leuprorelin serum levels of patients with renal and hepatic dysfunction were within the range of patients with healthy kidneys and liver. In chronic renal failure, high leuprorelin serum levels were measured in some cases. However, there is no sufficient data to show this observation appears to clinical relevance.

When 11.25 mg, as leuprorelin acetate, was administered subcutaneously to patients (in status of post surgery) with premenopausal breast cancer two times at 12-week intervals (concomitantly with tamoxifen citrate 20 mg/day), the blood concentration (the unchanged compound and its metabolite M-I) was as shown below. The blood concentrations fluctuated mostly at 0.2 ng/mL from 16 weeks after administration, when it reached the steady state, to 24 weeks after administration.



In children:

Figure 1 presents the leuprorelin serum levels in children during the first 6 months of treatment following s.c. administration of leuprorelin acetate 3-month depot (two injections).

From the first injection, the leuprorelin 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).

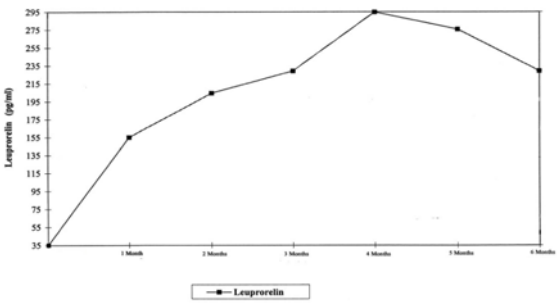


Figure 1: Leuprorelin serum levels during the first six months of treatment with the leuprorelin acetate 3-month depot formulation (two s.c. injections)

(n=42-43)

CLINICAL STUDIES

Prostate cancer

In a multicenter, opened, parallel, randomized, non-inferiority, comparative clinical study for prostate cancer patients who reach stable antitumor effect after monthly Leuplin Depot 3.75mg treatment, treated with Leuplin Depot 3Mevery 12 weeks or monthly Leuplin Depot 3.75mg every 4 week for 24 weeks.
The primary endpoint for the trial is the castration level maintenance rate at 0 to 24 weeks, i.e. the serum testosterone level at 0 to 24 weeks is maintained at below the pre-determined castration level in the protocol (≦100 ng/dL). The per-protocol population (PP) refers to the randomized subjects in serious violation of the protocol and with at least one serum testosterone level taken following randomization. The intent-to-treat population (ITT) refers to all randomized subjects.
Analysis and statistics in this trial are performed by calculating the two-sided 95% confidence interval in the two groups' differences in the castration level maintenance rate (3M – 1M). If the lower confidence bound of the 95% confidence interval is greater than the pre-determined non-inferiority critical value, -7%, it can be claimed that this product (Leuplin Depot 3M) has a castration effect not inferior to 3.75 SC Injection. The castration efficacy results based on the serum testosterone level are shown in the following table.

Castration Level	analyzed groups	Treatment	Maintenance cases of castration level	Maintenance rate of castration level (95% CI)	Two-sided confidence interval(3M－1M)
≦100ng/dL	PP	3M	46/46	100% (92.3%, 100%)	(-7.71%, 7.87%)
		1M	45/45	100% (92.1%, 100%)	
≦100ng/dL	ITT	3M	50 /51	98% (89.55%, 99.95%)	(-10.3%, 5.35%)
		1M	50/50	100% (92.9%, 100%)	
≦50 ng/dL	PP	3M	44/46	95.7% (85.16%, 99.47%)	-2.1%
		1M	44/45	97.8% (88.23%, 99.94%)	(-9.45%, 5.17%)
≦50 ng/dL	ITT	3M	48 /51	94.1% (83.76%, 98.77%)	-3.9 %
		1M	49/50	98% (89.35%, 99.95%)	(-11.4%, 3.65%)

Endometriosis and Uterine Leiomyomata (Fibroids)

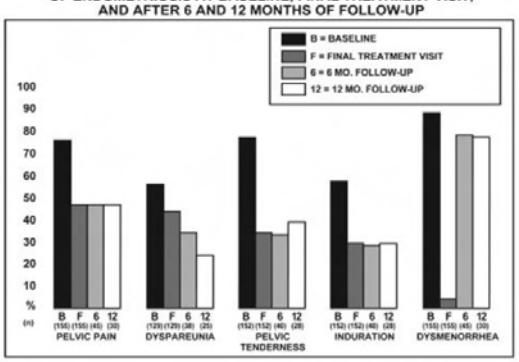
In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing.
By the third week following the injection, the mean estradiol concentration (8 pg/mL) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.
Serum estradiol was suppressed to ≤20 pg/mL in all subjects within four weeks and remained suppressed (≤40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.
LEUPLIN DEPOT 3M induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the injection and in a few subjects at later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.
LEUPLIN DEPOT 3M produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of monthly LEUPLIN DEPOT 3.75 mg during the controlled clinical trials for the management of endometriosis and the anemia caused by uterine fibroids.

Endometriosis

In a Phase IV pharmacokinetic/pharmacodynamic study of patients, LEUPLIN DEPOT 3M (N=21) was shown to be comparable to monthly LEUPLIN DEPOT 3.75 mg (N=20) in relieving the clinical signs/symptoms of endometriosis (dysmenorrhea, non-menstrual pelvic pain, pelvic tenderness and pelvic induration). In both treatment groups, suppression of menses was achieved in 100% of the patients who remained in the study for at least 60 days. Suppression is defined as no new menses for at least 60 consecutive days.
In controlled clinical studies, monthly LEUPLIN DEPOT 3.75 mg for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy.
The clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.
monthly LEUPLIN DEPOT 3.75 mg induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of patients, respectively, excluding those who became pregnant.
Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during the two controlled clinical studies. A total of 166 patients received monthly LEUPLIN DEPOT 3.75 mg.

Seventy-five percent (N=125) of these elected to participate in the follow-up period. Of these patients, 36% and 24% are included in the 6 month and 12 month follow-up analysis, respectively. All the patients who had a pain evaluation at baseline and at a minimum of one treatment visit, are included in the Baseline (B) and final treatment visit (F) analysis.

FIGURE 1 – PERCENT OF PATIENTS WITH SIGN/SYMPTOMS OF ENDOMETRIOSIS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP

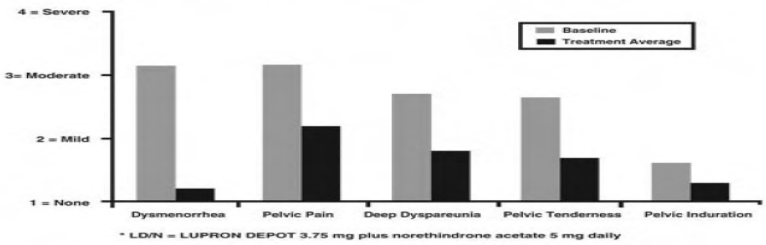


Hormonal add-back therapy

Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LEUPLIN, without compromising the efficacy of LEUPLIN in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with monthly LEUPLIN DEPOT 3.75 mg alone and 55 women treated with monthly LEUPLIN DEPOT 3.75 mg plus norethindrone acetate 5 mg (LD/N) daily. The second study was an open label study in which 136 women were treated with monthly LEUPLIN DEPOT 3.75 mg plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 Illustrates the mean pain scores for the LD/N group from the controlled study.

Figure 2
Treatment Period Mean Pain Scores For LD/N* Patients



* LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily

Uterine Leiomyomata (Fibroids)

Monthly LEUPLIN DEPOT 3.75 mg for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of monthly LEUPLIN DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two and three months respectively, 71% and 75% of patients met this criterion (Table 10). These data suggest however, that some patients may benefit from iron alone or 1 to 2 months of mothnly LEUPLIN DEPOT 3.75 mg.

Table 10: PERCENT OF PATIENTS ACHIEVING HEMATOCRIT ≥ 36% AND HEMOGLOBIN ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
LUPRON DEPOT 3.75 mg with Iron (N=104)	40*	71†	75*
Iron Alone (N=98)	17	39	49

* P-Value < 0.01

† P-Value < 0.001

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of patients at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of patients at final visit.

In this same study, a decrease of ≥25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. Monthly LEUPLIN DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

In addition, posttreatment follow-up was carried out in one clinical trial for a small percentage of monthly LEUPLIN DEPOT 3.75 mg patients (N=46) among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LEUPLIN®.

Premenopausal breast cancer

The following table shows the antitumor effect (the effectiveness rate) and the inhibition rate of serum estradiol concentration at the menopausal level observed in a clinical study in which 11.25 mg as Leuprorelin Acetate was subcutaneously administered to premenopausal breast cancer patients once every 12 weeks (concomitantly with tamoxifen citrate 20 mg/day).

Subject patients	Frequency of administration	Administration/ observation period	Antitumor effect (effectiveness rate)[Note 7)]	Inhibition rate of menopausal level [Note 8)]
Premenopausal advanced/recurrent breast	Twice	24 weeks	22.7% (5 cases/22 cases)	-

cancer cases				
Post (premenopausal breast cancer) surgery cases	Twice	24 weeks	-	98.4% (61 cases/62cases)

Note 7) Evaluation at 24 weeks of administration according to the "therapeutic effect assessment criteria of premenopausal advanced/recurrent breast cancer". (Best Response)
The effectiveness rate shows the ratio of CR+PR cases. (CR: Complete Response, PR: Partial Response)
Note 8) Ratio of cases whose serum estradiol concentration was under menopausal level (30 pg/mL) at 24 weeks of administration.

The recurrence-free survival rate in the clinical studies in which 11.25 mg as Leuprorelin Acetate was administered up to 96 weeks to 71 of the above patients in status of post (premenopausal breast cancer) surgery was 93.5%.
In a randomized controlled study conducted abroad (in Europe) in which Leuprorelin Acetate 11.25 mg at 3-month intervals or CMF therapy was given to patients who were positive for lymph node metastasis and were in status of post (premenopausal/perimenopausal breast cancer) surgery, relapse-free survival rates were shown as follows.

Drugs	Dosage and administration	Recurrence -free survival rate 2 years after start of treatment (primary endpoint)	Recurrence -free survival rate 5 years after start of treatment (secondary endpoint)
Leuprorelin Acetate 11.25 mg	subcutaneous injection at 3-month intervals for 24 months	83.0% (224/270 cases)	60.5% (153/253 cases)
CMF therapy cyclophosphamide 500mg/m2, methotrexate 40 mg/m2, fluorouracil 600 mg/m2	1 cycle [each drug given intravenously twice monthly (on the 1st and 8th days)] x 6 times (6 months)	80.9% (207/256 cases)	60.6% (146/241 cases)

PHARMACOLOGY

1. Mechanism of action

Repeated administration of either LH-RH in a massive dose or leuprorelin acetate, which is a highly potent LH-RH derivative, causes a transient pituitary - gonad system stimulating effect (acute effect) immediately after the first administration and then suppresses both the production and release of gonadotropin in the pituitary. It further suppresses the response of the testis to gonadotropin, resulting in a decrease in testosterone producing action (chronic effect). The LH releasing activity of Leuprorelin Acetate is approximately equal to 100 times that of LH-RH, and its action of suppressing the pituitary - gonad function is stronger than that of LH-RH. Since Leuprorelin Acetate is a highly potent LH-RH derivative, its strong action of suppressing the pituitary - gonad function is attributed to its higher resistance to proteolytic enzymes and higher affinity for LH-RH receptors in comparison with LH-RH. Moreover, since LEUPLIN is a sustained release preparation, it constantly releases Leuprorelin Acetate into the blood to effectively reduce the response of the testis, producing a highly favorable pituitary - gonad inhibitory action.

2. Action on gonadotropic hormone suppression

(1) In patients with prostate cancer, subcutaneous administration of Leuprorelin Acetate once every 12 weeks causes serum testosterone to fall below the castration level, indicating a pharmacological castrating effect.

(2) In patients with premenopausal breast cancer, subcutaneous administration of Leuprorelin Acetate once every 12 weeks causes serum estradiol to fall almost below the menopausal level, indicating a ovarian function inhibition effect. Ovulation is generally inhibited and menstruation is stopped.

(3) Reversible suppression of pituitary gonadotropin release occurs, with a subsequent decrease in estradiol (E2) or testosterone levels to values in the pre-pubertal range.

Initial gonadal stimulation (flare-up) may cause vaginal bleeding in girls who are already post-menarchal at start of treatment. Withdrawal bleeding may occur at the start of treatment. The bleeding normally stops as treatment continues.
The following therapeutic effects can be demonstrated:
- Suppression of basal and stimulated gonadotropin levels to pre-pubertal levels;
- Suppression of prematurely increased sexual hormone levels to pre-pubertal levels and arrest of premature menstruation;
- Improvement/normalization of the ratio of chronological age to bone age;
- Prevention of progressive bone age acceleration;
- Decrease of growth velocity and its normalization;
- Increase in final height.

Treatment result is the suppression of the pathologically, prematurely activated hypothalamic-pituitary-gonadal axis according to pre-pubertal age.
In a long-term clinical trial in children treated with leuprorelin at doses up to 15mg monthly for > 4 years resumption of pubertal progression were observed after cessation of treatment. Follow up of 20 female subjects to adulthood showed normal menstrual cycles in 80% and 12 pregnancies in 7 of the 20 subjects including multiple pregnancies for 4 subjects

PHYSICOCHEMISTRY

Structural formula (amino acids sequence):
5-oxo-Pro-His-Trp-Ser-Tyr-$_{D}$-Leu-Leu-Arg-Pro-NH-CH_2-CH_3・CH_3COOH
Nonproprietary name:
Leuprorelin Acetate [JAN]
Chemical name:
5-oxo-prolyl-histidyl-tryptophyl-seryl-tyrosyl-$_{D}$-leucyl-leucyl-arginyl-*N*-ethyl-prolinamide monoacetate
Molecular formula:
$C_{59}H_{84}N_{16}O_{12}$・$C_2H_4O_2$
Molecular weight:
1269.45
Description:
Leuprorelin Acetate occurs as a white to yellowish white powder. It is freely soluble in water and acetic acid(100), soluble in methanol and ethanol(95), slightly soluble in absolute ethanol(99.5) and sparingly soluble in acetonitrile. It is hygroscopic.

PACKAGING

1 kit