Microencapsulated sustained release

LH-RH derivative preparation

LEUPLIN®DEPOT 3.75mg S.C. Injection

(Leuprorelin acetate for injection)

(Note)1. It is a prescription-only drug
2. Use only pursuant to the prescription or directions of a physician, etc
Storage: Under 25℃.
Expiration date:
3 years. 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® is contraindicated in the following patients.)

Endometriosis, Uterine myoma, Central precocious puberty	(1) Patients with a history of hypersensitivity to any of the ingredients of this drug or synthetic LH-RH or LH-RH derivatives (2) Pregnant women or women having possibilities of being pregnant, or nursing mothers (See PRECAUTIONS 5. Use during Pregnancy, Delivery or Lactation.) (3) Patients with abnormal genital bleeding of indeterminable nature [There is a possibility of malignant disease.]
Premenopausal breast cancer	(1) Patients with a history of hypersensitivity to any of the ingredients of this drug or synthetic LH-RH or LH-RH derivatives (2) Pregnant women or women having possibilities of being pregnant, or nursing mothers (See PRECAUTIONS 4. Use during Pregnancy, Delivery or Lactation.)
Prostate cancer	Patients with a history of hypersensitivity to any of the ingredients of this drug or synthetic LH-RH or LH-RH derivatives

COMPOSITION

LEUPLIN® is a white lyophilizate supplied in a vial which contains the fillowing:
Leuprorelin cetate……3.75mg
Copolymer (DL-Lactic acid/Glycolic acid) (3:1)……33.75mg
D-Mannitol……6.6mg
Total……..44.1mg
The attached vehicle for suspension in one ampule(1ml)
Contains the following:
D-Mannitol……50mg
Carboxymethylcellulose sodium……5mg
Polysorbate 80……1mg
Water for injection add to……1ml

LEUPLIN® , when suspended with 1 ml of the attached vehicle for suspension, shows a pH value of 6.0 - 7.5 and an osmotic pressure ratio (relative to isotonic sodium chloride solution) of about 1.

INDICATIONS

○ Prostate cancer
○ Endometriosis
○ Central precocius puberty
○ Amelioration of symptoms in uterine myoma with hypermenorrhea, anemia etc. and is supposed to undergo myomectomy.
○ Premenopausal breast cancer

<Precautions for indication >

Uterine myoma	It should be noted that the treatment of uterine myoma with LEUPLIN® 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.
Premenopausal breast cancer	When starting treatment with LEUPLIN®, absence/presence of hormone receptor expression should be confirmed as a rule. When hormone receptor expression is confirmed to be negative, LEUPLIN® should not be used.

DOSAGE AND ADMINISTRATION

- For endometriosis
  Usually, for adults, 3.75 mg of leuprorelin acetate is subcutaneously administered once every 4 weeks.
  The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.
  The recommended treatment period is 6 months.
- For uterine myoma
  Usually, for adults, 1.88 of leuprorelin acetate is subcutaneously administered once every 4 weeks.

  Dosage can be appropriately adjusted according to the symptoms of the patient. The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.

- For prostate cancer and premenopausal breast cancer
  Usually, for adults, 3.75 mg of leuprorelin acetate is subcutaneously administered once every 4 weeks.
- Central precocious puberty
  Usually, a dose of 30 μg/kg of leuprorelin acetate is subcutaneously administered once every 4 weeks. Depending upon the patient's condition, the dosage may be increased up to 90 μg/kg.

Before administration, the content of one vial should completely be suspended with the attached 1 ml of vehicle for suspension, with caution againt faoming.

<Precautions for dosage and administration>

For all indications

Since LEUPLIN® is a sustained release preparation with its action lasting 4 weeks, administration at an interval exceeding 4 weeks may lead to the recurrence of an increase in the serum level of gonadotropic hormone 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 4 weeks should be observed.

Endometriosis, Uterine myoma	(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. (See CLINICAL STUDIES.) (2) Before starting treatment with LEUPLIN®, 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®, 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®. 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.) 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®, 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 to estrogen reducing effect of LEUPLIN®. Therefore, when it is inevitable to administer this drug for a long period, the drug should be carefully administered after bone mass is examined as far as possible.

PRECAUTIONS

1. **Careful Administration** (LEUPLIN® should be administered with care in the following patients.)

Endometriosis, Uterine myoma, Premenopausal breast cancer	Patients with submucous myoma [Bleeding symptom may be aggravated.] (See 2. Important Precautions.)
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.]

2. **Important Precautions**

Endometriosis	(1) In administration of LEUPLIN®, care should be taken to differentiate a similar disease (malignant tumor, etc.) from endometriosis. If, during administration of LEUPLIN®, 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®, 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. (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)
Uterine myoma	(1) In administration of LEUPLIN®, care should be taken to differentiate a similar disease (malignant tumor, etc.) from uterine myoma. If, during administration of LEUPLIN®, any growing phyma is found or no improvement is seen in the clinical symptom, the administration should be discontinued. (2) In administration of LEUPLIN® 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®, 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.)
	(1)Since LEUPLIN® is an agent for endocrine therapy, use of this drug for premenopausal

Premenopausal breast cancer	breast cancer should be limited to patients for whom treatment with LEUPLIN® is considered appropriate under the supervision of a physician who has adequate knowledge and experience in medication for cancer. (2) In the early period after the first administration of LEUPLIN®, 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 bone pain, etc. In such a case, symptomatic treatment should be given. (3) If antitumor effect is not obtained with LEUPLIN® and any progression of the tumor is observed, the administration should be discontinued. (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.)
Prostate cancer	(1)Since LEUPLIN® is an agent for endocrine therapy, use of this drug for prostate cancer should be limited to patients for whom treatment with LEUPLIN® is considered appropriate under the supervision of a physician who has adequate knowledge and experience in medication for cancer. (2)In the early period after the first administration of LEUPLIN®, a transient elevation of the serum level of testosterone 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 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.
Central precocious puberty	(1) In the early period after the first administration of LEUPLIN®, a transient elevation of the serum level of gonadotropic hormone 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. (2) During the treatment with LEUPLIN®, LH-RH test should be performed at regular intervals. When suppression of the action of LH and FSH in blood is not achieved, the administration of this drug should be discontinued.

3. Drug Interactions

Endometriosis, Uterine myoma

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

The following table shows the incidence of adverse reactions, including abnormalities in laboratory data, according to the indicated diseases and phase of investigation.

Indicated diseases	Investigation before approval	Postmarketing investigation of the results of drug use
Endometriosis	86.3% [472/547]	31.1% (803/2,586) (as of December 1998)
Uterine myoma	83.5% [344/412]	19.4% (485/2,498) (as of December 2000)
Premenopausal breast cancer	64.0% [64/100]	11.6% (34/292) (as of December 2000)
Prostate cancer	47.5% [75/158]	10.3% (127/1,232) (as of December 1998)
Central precocious puberty	20.8% [22/106]	3.5% (3/85) (as of December 1998)

In parentheses: The number of patients with adverse reactions/the number of patients accepted for the evaluation of safety

The adverse reactions listed below have been observed in the above investigations, spontaneous reports, etc.
Since LEUPLIN is a sustained release preparation, the patient's condition should be observed while the effect of this drug lasts after the final dosing.

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.

(1) Clinically significant adverse reactions

For 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®. 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.

Endometriosis, Uterine myoma, 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.
Prostate cancer	(1) Since a depressed state occurr(< 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, uch as discontinuation of administration, should be taken.

(2) Other adverse reactions

Endometriosis, uterine myoma, premenopausal breast cancer, central precocious puberty

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

	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	Stiffness of fingers or other joints 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, 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		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	Weight decrease, taste abnor-mality or abnormal thyroid function

		extremities, respiratory distress, fever, increased total cholesterol, LDL cholesterol or triglyceride, or hyperkalemia.	

Note 1) Close observation should be made.

Prostate cancer

	≧ 5%	0.1% - < 5%	< 0.1%
1) Hepatic[Note 1)]	Increased LDH	Jaundice, or increased AST(GOT), ALT(GPT), γ-GTP or ALP	
2) Endocrine	Hot flushes, feeling of warmth	Headache, insomnia facial hot flushes, dizziness, diaphoresis, decreased libido, erectile disturbance, gynecomastia, testicular atrophy or discomfort in the perineal region	
3)Musculo-skeletal		Arthralgia, bone pain, pain in the shoulder, low back or limbs, difficulty in walking stiffness of fingers or other joints.	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 anorexia or constipation.	Diarrheal
9)Hypersensitivity		Rash or pruritus	
10)Administration site		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.

5. Use during Pregnancy, Delivery or Lactation

Endometriosis, Uterine myoma, Premenopausal breast cancer, Central precocious puberty	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.]

6. Pediatric Use

Central precocious puberty

The safety of LEUPLIN® in prematures, newborns and nursing infants has not been established.

7. Precautions concerning Use

For all indications

(1) Route of administration

LEUPLIN® should be used only by the subcutaneous route.

[Intravenous injection of LEUPLIN® may induce thrombosis.]

(2) Method of administration

1) A needle for injection of 23 gauge should be used.

2) For subcutaneous injection, the following cautions should be exercised.

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

(3) Preparation

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

2) If any sedimentation is noticed in the suspension of vial product, such suspension should be used after swirling gently, avoiding formation of bubbles, to resuspend the particles uniformly.

8. Other Precautions

For 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.[2)]

Endometriosis, uterine myoma, premenopausal breast cancer, central precocious puberty

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

Prostate cancer

It has been reported that the administration of LEUPLIN® brought about cerebral infarction, venous thrombosis or pulmonary embolism.

PHARMACOKINETICS

Endometriosis

1. Blood concentrations

Fig. 1 shows blood concentration in a study in which 1.88 mg or 3.75 mg, as leuprorelin acetate, was administered subcutaneously to patients with endometriosis in a total of six times at 4-week intervals. When 3.75 mg, as leuprorelin acetate, was administered subcutaneously to patients with endometriosis (77 patients) six times at 4-week intervals, the combined blood concentration of the unchanged compound and metabolite M-I※ revealed no accumulation.

※ M - I: Tyr - $_{D}$ - Leu - Leu - Arg - Pro - NHC_2H_5

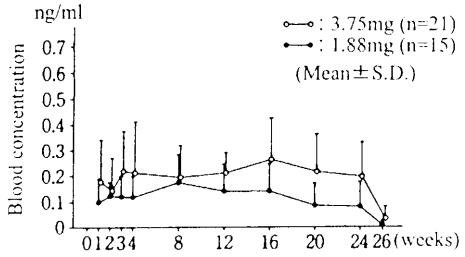

Fig.1 Blood concentration of leuprorelin acetate
(in administration to patients with endometriosis)

2. Urinary excretion

The following table shows the urinary excretion rates (%) of the unchanged compound and metabolite M-I at 24 hours after the first administration and 24 hours after the sixth administration, when 3.75 mg, as leuprorelin acetate, was administered subcutaneously to patients with endometriosis six times at 4-week intervals:

24 hours after the first administration		24 hours after the sixth administration	
Unchanged compound	Metabolite M-I	Unchanged compound	Metabolite M-I
1.1 (8)	1.1 (8)	1.3 (7)	1.3 (7)

Figures show the urinary excretion rate (%), and those in parentheses the number of patients.

Uterine Myoma

The pharmacokinetics in patients with uterine myoma are considered to be the same as those in patients with endometriosis, which is the same estrogen dependent disease as uterine myoma and is occurring in nearly the same age group as uterine myoma.

Premenopausal breast cancer

When 3.75 mg, as leuprorelin acetate, was administered subcutaneously to patients with premenopausal breast cancer three times at 4-week intervals, the blood concentration of the unchanged compound was as shown in Fig. 2. The blood concentrations at 4 weeks after the second and third administration were not higher than the level observed 4 weeks after the first administration. Thus, this drug is not likely to accumulate.

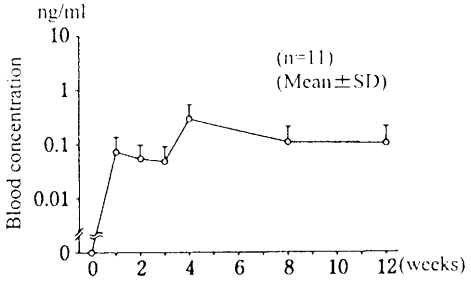

Fig.2 Blood concentration of leuprorelin acetate
(in administration to patients with premenopausal breast cancer)

Prostate Cancer

1. Blood concentrations

Fig. 3 shows the blood concentration of the unchanged compound when a single subcutaneous dose of 3.75 mg, as leuprorelin acetate, was administered to patients with prostate cancer. The blood concentrations of the unchanged compound in subcutaneous administration of 3.75 mg, as leuprorelin acetate, to patients with prostate cancer (17 patients) three times at 4-week intervals, revealed no accumulation.

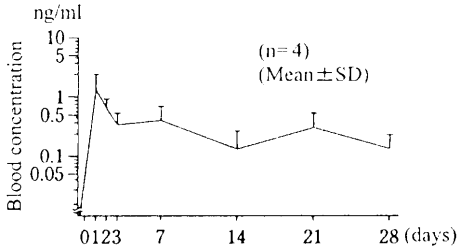

Fig. 3 Blood concentration of leuprorelin acetate
(in administration to patients with prostate cancer)

2. Urinary excretion

When a single dose of 3.75 mg, as leuprorelin acetate, was subcutaneously administered to patients with prostate cancer (2 patients), the urinary excretion rates of the unchanged compound and its metabolite M-I up to 28 days after administration were 2.9% and 1.5%, respectively.

Central precocious puberty

1. Blood concentrations

Fig. 4 shows the blood concentrations of the unchanged compound after the first administration, when 30 μg/kg, as leuprorelin acetate, was given subcutaneously to patients with central precocious puberty twelve times at 4-week intervals. Judging from the trend of blood concentration of the unchanged compound, this drug is not considered to accumulate.

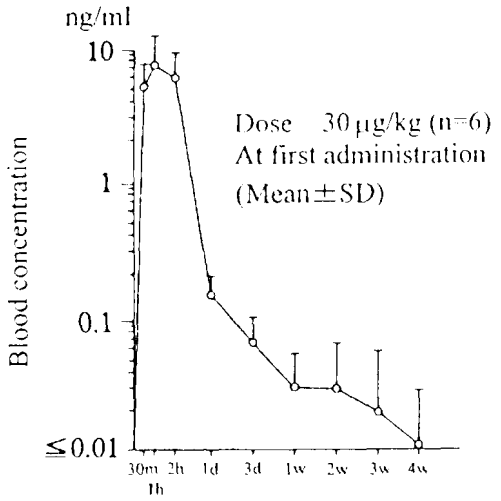

Fig.4 Blood concentration of leuprorelin acetate
(in administration to patients with central precocious puberty)

2. Urinary excretion

When a single dose of 30 μg/kg, as leuprorelin acetate, was subcutaneously administered to patients with central precocious puberty (1 patient), the urinary excretion rates of the unchanged compound and its metabolite M-I up to 28 days after administration were 1.8% and 7.1%, respectively.

CLINICAL STUDIES

Endometriosis

In clinical studies in which 3.75 mg of leuprorelin acetate was administered subcutaneously to patients with endometriosis six times at 4-week intervals, the global improvement rating at week 24 was as shown in the following table. With administration of 3.75 mg, the improvement rate (marked improvement + improvement) was 79.9%.

		1.88mg Marked improvement + Improvement (Improvement rate)	3.75mg Marked improvement + Improvement (Improvement rate)
Body weight	< 50 kg	20/28 (71.4)	107/136 (78.7)
	≧50 kg	31/49 (80.7)	59/197 (80.7)

Figures show the number of patients, and those in parentheses show %.

As compared with 3.75mg, the clinical effect of 1.88mg was slightly lower. However, it was suggested that when compared based on body weight, nearly the same improvement rate would be obtained where the body weight is less than 50kg.

In furhter clinical studies in which 1.88mg of leuprorelin acetate was administered subcutaneously six times at 4-week intervals to patients with endometriosis weighing less than 50kg, the improvement rate (marked improvement + improvemnet) was 82.0% (41/50 patients). The double-blind comparative study in patients with endometriosis has proved the usefulness of LEUPLIN®.

Uterine myoma

In a clinical study in which 1.88 mg or 3.75 mg of leuprorelin acetate was administered subcutaneously to patients with uterine myoma four or six times at 4-week intervals, the global improvement rating (marked improvement + improvement) and the marked improvement rating at 4 weeks after the final administration, excluding indeterminable cases, were 83.5% (259/310 patients) and 39.7% (123/310 patients), respectively.

The following table shows the improvement rate (marked improvement + improvement) in stratified analysis by dose, body weight and preadministration size of uterus (by vaginal examination). In patients with relatively heavy weight (55kg or more) and those with markedly enlarged uterus (fist size or larger), the improvement rate was higher in 3.75 mg group than in 1.88 mg group.

		Marked improvement + Improvement (Improvement rate)		Testing results (χ^2 test)
		1.88 mg	3.75 mg	
Body weight	< 55 kg	49/58 (84.5)	110/127 (86.6)	N.S.
	≧55 kg	20/32 (62.5)	80/92 (87.0)	p<0.01
Size of uterus(vaginal examination)	Smaller than fist size	12/14 (85.7)	53/66 80.3)	N.S.
	Fist size or larger	23/32 (71.9)	100/113 (88.5)	p< .01

Figures show the number of patients, and those in parentheses show %.

The double-blind comparative study in patients with uterine myoma has proved the usefulness of LEUPLIN®. In the meantime, in a dose-setting study in which this drug was administered four times in doses of 0.94 mg, 1.88 mg, 3.75 mg and 5.63 mg, adverse reactions including changes in laboratory values were observed in 35 of 48 patients (72.9%), 36 of 45 patients (80.0%), 39 of 43 patients (90.7%) and 43 of 49 patients (87.8%), respectively.

Premenopausal breast cancer

In a clinical study in which 3.75 mg of leuprorelin acetate was administered subcutaneously to patients with premenopausal breast cancer three times at 4-week intervals, the effectiveness rate (CR + PR) at week 12 in complete cases and evaluable cases were 30.4% (14/46 patients) and 28.6% (14/49 patients), respectively. In addition, this drug continued to be used alone after week 12, and the effectiveness rate※ (CR + PR) in complete cases and evaluable cases covering those for which evaluation could be made for long - term administration and those for which evaluation was finished at week 12 were 37.0% (17/46 patients) and 34.7% (17/49 patients), respectively (※Evaluation based on "Best response" noted in the entire observation period). [Evaluation according to the "Criteria for evaluation of therapeutic effect in advanced and recurrent breast cancer" (CR: Complete Response (markedly effective), PR: Partial Response (effective))]

Prostate cancer

In a clinical study in which 3.75 mg of leuprorelin acetate was administered subcutaneously to patients with prostate cancer three times at 4-week intervals, the effectiveness rate (CR + PR) at week 12 in complete cases was 53.9% (55/102 patients) and that in evaluable cases was 48.2% (55/114 patients). In a long-term clinical study in which this drug was subcutaneously administered 5 to 46 times at 4 - week intervals to patients who were given continuous treatment with this drug alone, the effectiveness rate※ (CR + PR) of complete cases against evaluable cases was 51.7% (15/29 patients). (※Evaluation based on "Best response" noted in the entire observation period.) [Evaluation according to the "Criteria for evaluation of therapeutic effect in medicinal treatment for prostate cancer" (CR: Complete Response (markedly effective), PR: Partial Response (effective))]

The comparative clinical study in patients with prostate cancer has proved the usefulness of LEUPLIN®.

Central precocious puberty

In a clinical study in which 30 μg/kg to 90 μg/kg of leuprorelin acetate was administered subcutaneously to patients with central precocious puberty once every 4 weeks, the effectiveness rates at week 24, week 48, week 96 and week 114 were as shown in the following table:

Evaluation time	No. of patients	Markedly effective (Effectiveness rate)	Markedly effective + Effective (Effectiveness rate)
Week 24	102	37 (36.3)	92 (90.2)
Week 48	100	33 (33.0)	90 (90.0)
Week 96	92	30 (32.6)	84 (91.3)
Week 144	23	9 (39.1)	22 (95.7)

Figures show the number of patients, and those in parentheses show %.

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 ovary and testis to gonadotropin, resulting in a decrease in estradiol and 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 ovary and testis, producing a highly favorable pituitary - gonad inhibitory action.

2. Action on gonadotropic hormone suppression

(1) In patients with endometriosis, uterine myoma or premenopausal breast cancer, subcutaneous injection of leuprorelin acetate once every 4 weeks generally causes serum estradiol to fall to a value near the menopausal level. Thus, this drug produces an ovarian function suppressing effect, with resultant inhibition of normal ovulation and cessation of menstruation.

(2) In patients with prostate cancer, subcutaneous administration of leuprorelin acetate once every 4 weeks causes serum testosterone to fall below the castration level, indicating a pharmacological castrating effect.

(3) In girl and boy patients with central precocious puberty, subcutaneous administration of leuprorelin acetate, once every 4 weeks, reduces the serum level of gonadotropic hormone to the prepubertal level, exhibiting an action of delaying the progression of secondary sex characteristics.

DESCRIPTION

Physicochemical properties of the active ingredient:

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:

$C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$

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 ethanol (99.5) and sparingly soluble in acetonitrile. It is hygroscopic.