(เอกสารกำกับยา)

ENANTONE® L.P. 1.88 mg

(LEUPRORELIN ACETATE FOR SUSTAINED RELEASE SUSPENSION)

DESCRIPTION

ENANTONE® L.P. 1.88 mg is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or (LH-RH)). The analog possesses greater potency than the natural hormone.

COMPOSITION

For vial and ampule

Each vial contains 1.88 mg leuprorelin acetate as lyophilized microcapsules.

Each ampule contains 2ml sterile vehicle which is used to reconstitute *ENANTONE® L.P. 1.88 mg* powder for administration to the patient.

For Dual Chamber Pre-filled Syringe (DPS) with a needle (25 G)

Each DPS contains 1.88 mg leuprorelin acetate and 1ml sterile vehicle. The DPS is a dual chamber syringe with white powder in the front chamber and clear, colorless fluid in the rear chamber.

INDICATION

- Endometriosis
- Decrease of fibroid (myoma) volume and/or amelioration of symptoms in uterine fibroids with hypermenorrhea, hypogastralgia, low back pain, anemia, etc.

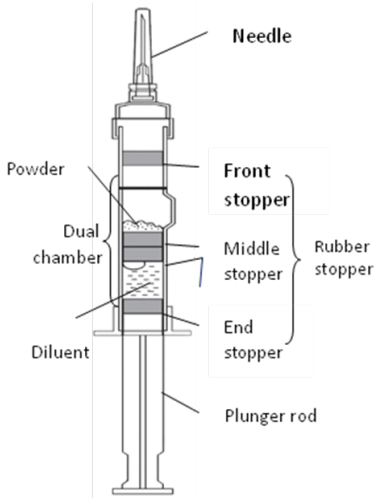
DOSAGE AND ADMINISTRATION

The lyophilized microcapsules of *ENANTONE® L.P. 1.88 mg* are to be reconstituted and administration with the following directions:

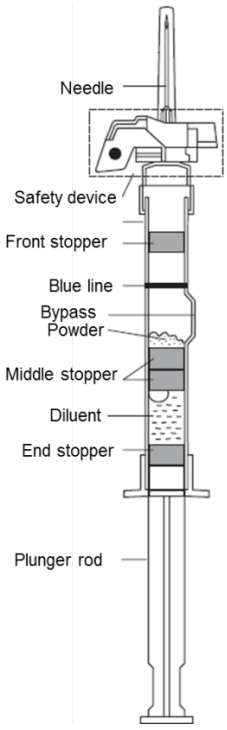
For vial and ampule

1. Using a syringe with a 23-gauge needle, withdraw 2 ml of vehicle from ampule, and inject it into the vial.
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire content of the vial into the syringe and inject it at the time of reconstitution as single subcutaneous or intramuscular injection **once a month.**

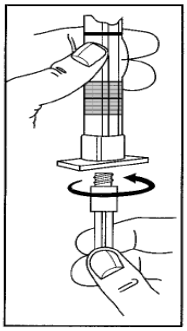
For Dual Chamber Pre-filled Syringe (DPS) with a needle;
For Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle
Powder and fluid must be mixed before use. Read and follow the instructions below.



Dual Chamber Pre-filled Syringe)DPS(with a needle

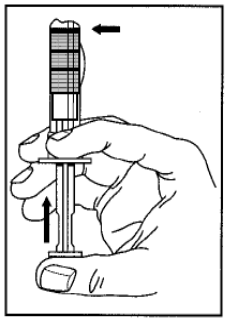


Dual Chamber Pre-filled Syringe and Safety Device)DPS-SD(with a needle

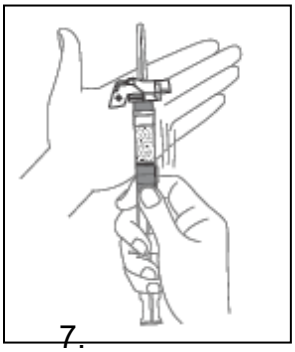


1. To prepare for an injection, screw the plunger rod into the end stopper of the syringe.
2. Ensure that the needle is properly fastened to the syringe.
   NOTE: Never pull back the plunger rod during the following process.

3. Tap gently on the syringe to ensure that there are no large quantities of powder remaining on the chamber wall.



4. Hold the syringe upright with the tip of the needle upwards. Push the plunger in slowly (approximately 6-8 seconds) until the front edge of the middle rubber stopper reaches the blue line in the middle of the syringe and the fluid starts to mix with the powder.
   NOTE: Pushing the plunger rod quickly or over the blue line will cause leakage of the suspension from the needle.



7.

5. Hold the syringe upright. Mix the powder and fluid thoroughly by shaking gently or rolling the syringe between your palms to ensure a uniform suspension. The suspension has a milky appearance.
6. If powder sticks to the rubber stopper, tap the syringe gently with your finger.

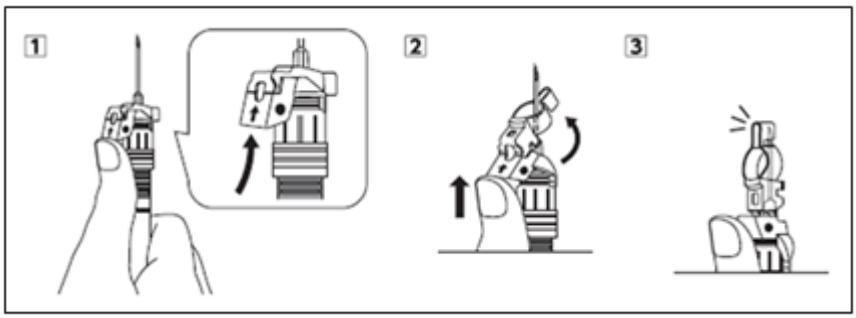
   NOTE: Avoid hard tapping to prevent generation of bubbles.

7. Hold the syringe upright. With the other hand, pull the needle cap upwards without twisting.
8. Hold the syringe upright. Push the plunger forwards to expel all air from the syringe.
9. Inject the entire contents of the syringe **subcutaneously** (e.g. into abdomen, thigh or gluteal region) **or intramuscularly** immediately after preparation. Make sure the injection is not given into a blood vessel. As the suspension settles very quickly following preparation, *ENANTONE® L.P. 1.88 mg DPS* must be mixed and used immediately.

10. The patient must be instructed not to massage the injection site.

Although the suspension has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

For Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle
AFTER INJECTION, withdraw the needle from the patient and immediately activate the safety device to cover the needle by pushing the arrow forward with a finger until a CLICK is heard and the device is fully extended and the needle is covered



After reconstitution, 1.88 mg of leuprorelin acetate is administered once a month as a single subcutaneous or intramuscular injection. As with other drugs administered regularly by injection, the injection site should be varied periodically.

- **Treatment with Endometriosis**
  Usually, for adults, 3.75 mg of leuprorelin acetate is **subcutaneously or intramuscularly administered once a month.** However, when the patient's weight is less than 50 kg, 1.88 mg preparation may be used.
  The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.

- **Treatment with Uterine fibroids**
  Usually, for adults, 1.88 mg of leuprorelin acetate is **subcutaneously or intramuscularly administered once a month.**
  However, for patients with heavy weight or those with markedly enlarged uterus, 3.75 mg is administered.

  The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.

CONTRAINDICATIONS

1. Hypersensitivity to leuprorelin, any of the excipients or other synthetic GnRH analogues or GnRH derivatives
2. Undiagnosed abnormal vaginal bleeding.

3. Use in women who are or may become pregnant while receiving the drug as *ENANTONE® L.P. 1.88 mg* may cause fetal harm when administered to pregnant women.

4. Use in women who are breast feeding. Because of the lack of data regarding *ENANTONE® L.P. 1.88 mg* excretion in milk and its potential effects on nursing babies, *ENANTONE® L.P. 1.88 mg* should not be used on nursing mother.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Since *ENANTONE® L.P. 1.88 mg* 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 loss of suppression of the pituitary-gonad system, resulting in a transient aggravation of the clinical condition. Therefore, the method of administering once a month should be observed.

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.
Prepare the injectable suspension at the time of use and, after reconstituting, use immediately.

Seizures:
Postmarketing reports of seizures have been observed in patients treated with leuprorelin acetate and these events have been reported in both children and adults, and in those with or without a history of epilepsy, seizure disorders or risk factors for seizures.

It should be noted that the treatment of uterine fibroids with *ENANTONE® L.P. 1.88 mg* 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.

Careful Administration: *ENANTONE® L.P. 1.88 mg* should be administered with care in the following patients.

- Patients with submucous fibroids [Bleeding symptoms, which may be severe, may be aggravated.]

In administration of *ENANTONE® L.P. 1.88 mg*, care should be taken to differentiate a similar disease (malignant tumor, etc.) from endometriosis and uterine fibroids. If, during administration of *ENANTONE® L.P. 1.88 mg*, any growing phyma is found or no improvement is seen in the clinical symptom, the administration should be discontinued.

Before starting treatment with this drug, pregnancy must be excluded (see contraindication). It is imperative the administration is initiated on the first to fifth day after the start of menstrual period. During the period of the treatment, the patient should be instructed to prevent conception with the use of non-hormonal methods.

In the early period after the first administration of *ENANTONE® L.P. 1.88 mg*, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of *ENANTONE® L.P. 1.88 mg*, as a highly active GnRH 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.

Long-term estrogen deprivation by bilateral oophorectomy, ovarian ablation or administration of GnRH analogues is associated with increased risk of bone mineral loss which, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture. Therefore, the duration of administration of this drug should be limited to 6 months. When it is necessary to resume administration of this drug, the bone mass should be examined as far as possible.

Prior to administration of leuprorelin acetate, undiagnosed abnormal vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated.

Inhibition of endogenous sex hormone production, such as during estrogen deprivation e.g. in menopausal females, is associated with metabolic changes e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes as well as an increased risk for cardiovascular disease. However, prospective data did not confirm a link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic changes or syndrome, or cardiovascular diseases should be appropriately monitored.

There is an increased risk of depression in patients undergoing treatment with leuprorelin acetate and patients should be monitored as appropriate.

In administration of *ENANTONE® L.P. 1.88 mg* to patients with submucous fibroids, bleeding symptoms, which may be severe, 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.

DRUG INTERACTIONS

Precautions for coadministration (*ENANTONE® L.P. 1.88 mg* 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 *ENANTONE® L.P. 1.88 mg* may be reduced.	*ENANTONE® L.P. 1.88 mg* exerts its therapeutic effects by reducing the secretion of sex hormones. Consequently, administration of sex hormones may reduce the therapeutic effect of this product.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Leuprorelin acetate can influence the ability to drive and use machines due to visual disturbances and dizziness.

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	Post-marketing investigation of the results of drug use

Endometriosis	86.3% [472/547]	31.1% (803/2,586) (as of December 1998)
Uterine fibroids	83.5% [344/412]	19.4% (485/2,498) (as of December 2000)

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.

(1) Clinically significant adverse reactions

1) Since interstitial lung disease, 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 *ENANTONE® L.P. 1.88 mg*. 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) As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma. Therefore, if headache, vision impairment, visual field disorder, etc. are observed immediately after the first dose of *ENANTONE® L.P. 1.88 mg* appropriate measures, such as surgical treatment, should be taken after conducting examination.

(2) **Other adverse reactions**

	≥ 5%	0.1% - < 5%	< 0.1%
Symptoms resulting from decreased estrogen	Hot flushes, feeling of warmth, feeling of hot flushes, shoulder stiffness, headache, insomnia, dizziness or diaphoresis	Decreased libido, coldness, libido disturbance or emotional lability	

	≥ 5%	0.1% - < 5%	< 0.1%
Female reproductive		Metrorrhagia, vaginal dryness, coital pain, vaginitis, increased fluor, ovarian hyperstimulation syndrome, or pain, swelling or atrophy of the breast	
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	
Dermatologic		Acne, dry skin, alopecia, hypertrichosis or nail abnormality	
Psychoneurologic		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia	
Hypersensitivity		Rash or pruritus	
Hepatic*		Increased AST(GOT), ALT(GPT), ALP, LDH, γ-GTP or bilirubin	Jaundice
Gastrointestinal		Nausea, vomiting, anorexia, abdominal pain, feeling of enlarged abdomen, diarrhea, constipation, stomatitis or thirst	
Cardiovascular		Palpitation or increased blood pressure*	
Hematologic		Red blood cell count increased, anemia, white blood cell decreased, platelet count decreased or prolonged partial thromboplastin time	
Urinary		Pollakiuria, dysuria or increased BUN	
Administration site		Reactions at the injection site, such as pain, induration and redness	Abscess
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

* Close observation should be made.

Endometriosis, uterine myoma, breast cancer

Immune system disorders:

Hypersensitivity, including anaphylactic reaction, urticaria, wheezing

Metabolism and nutrition disorders:

Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)

Psychiatric disorders:

Affect lability, depression, sleep disorder

Nervous system disorders:

Pituitary haemorrhage, seizure

Eye disorders:

Visual impairment

Hepatobiliary disorders:

Hepatic function abnormal (including jaundice)

Musculoskeletal and connective tissue disorders:

Myalgia, osteoporosis (including vertebral body fractures), muscular weakness

Reproductive system and breast disorders:

Breast atrophy, vulvovaginal dryness, vulvovaginitis, breast tenderness, vaginal hemorrhage

General disorders and administration site conditions:

Injection site reaction, edema, fatigue

USE IN PREGNANCY AND LACTATION

ENANTONE® L.P. 1.88 mg should not be administered to pregnant women, women having possibilities of being pregnant, or nursing mothers. [Abortion due to GnRH 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.]

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Enantone LP 1.88mg contains leuprorelin acetate, a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH) which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins which leads to a transient increase in gonadal steroid levels in both men and women. Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels. In men serum testosterone levels, initially raised in response to early luteinising hormone (LH) release, fall to castrate levels in about 2-4 weeks.

Leuprorelin acetate is inactive when given orally.

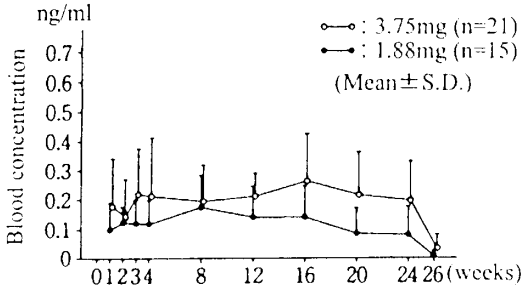
Pharmacokinetic Properties

Studies show that single intramuscular or subcutaneous doses of leuprorelin acetate over the dose range 3.75 to 15 mg results in detectable levels of leuprorelin acetate for more than 28 days, good bioavailability, a consistent and predictable pharmacokinetic profile, and biological efficacy at plasma levels of less than 0.5 ng/ml. The pharmacokinetic profile is similar to that seen in animal studies using the compound, with an initial high level of drug released from the microcapsules during reconstitution and injection followed by a plateau over a 2-3 week period before levels gradually become undetectable. There appears to be no significant difference between the routes of administration (im vs sc) in biological effectiveness or pharmacokinetics.

The metabolism, distribution and excretion of leuprorelin acetate in humans have not been fully determined.

Repeated subcutaneous administration of 1.88 mg or 3.75 mg leuprorelin acetate 1 month depot 4 weekly for 24 weeks in women with endometriosis did not result in accumulation of unchanged leuprorelin and its major metabolite MI. Serum concentrations are shown in Figure 1.

Figure 1. Serum concentrations of leuprorelin acetate and its major metabolite MI in women with endometriosis



Preclinical safety data

Animal studies have shown that leuprorelin acetate has a high acute safety factor. No major overt toxicological problems have been seen during repeated administration. Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long-term clinical studies. No evidence of mutagenicity or teratogenicity has been shown. Animal reproductive studies showed increased foetal mortality and decreased foetal weights reflecting the pharmacological effects of this GnRH agonist.

INCOMPATIBILITIES

No other fluid other than the sterile vehicle provided for *ENANTONE® L.P. 1.88 mg* can be used for the reconstitution of *ENANTONE® L. P. 1.88 mg* powder.

EXPIRATION PERIOD

3 years unopened. Once reconstituted with sterile vehicle, the suspension should be administered immediately.

CAUTIONS FOR STORAGE

Store below 30°C, avoiding heat, light. Protect from freezing.

After the expiry date indicated on the labeling, out of date product should be discarded.

PACKAGING

Vial with powder and ampule with 2ml vehicle

Dual chamber pre-filled syringe (DPS) with a needle (25 G)

Further information is available on request to Takeda (Thailand), Ltd.

Manufactured by

Takeda Pharmaceutical Company Limited

Hikari plant, Yamaguchi, Japan

Imported by

Takeda (Thailand), Ltd.

Bangkok, Thailand

Date of revision July 2020