ENANTONE L.P. 11.25 mg

Leuprorelin Acetate 3 Month Depot Injection

ENANTONE L.P. 11.25 mg is a sterile, lyophilized, white, odorless PLA (poly DL-lactic acid) microsphere powder for subcutaneous or intramuscular injection after reconstitution with the sterile vehicle to provide a 3 month depot injection.

COMPOSITION

For vial and ampoule

Each vial contains 11.25 mg leuprorelin acetate as lyophilized microcapsules.

Each ampoule contains 2ml sterile vehicle which is used to reconstitute *ENANTONE L.P. 11.25 mg* powder for administration to the patient.

For Dual Chamber Pre-filled Syringe (DPS) with a needle (23 G)

Each DPS contains 11.25 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

- **Prostate cancer**
  - *Metastatic prostate cancer*
  - *Locally advanced prostate cancer, as an alternative to surgical castration*
  - *As an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer*
  - *As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression*
- **Endometriosis** at genital and extra-genital localization (from stage I to stage IV)
  - *Symptomatic laparoscopically confirmed endometriosis, when suppression of ovarian hormone production is indicated, provided the disease does not primarily require surgery.*
  - *Preoperative flattening of the endometrium before planned operative hysteroscopic intervention, e.g. endometrium ablation or resection.*
- **Symptomatic Uterine Fibroids (Leiomyomata)**, when suppression of ovarian hormone production is indicated, as a preoperative measure for the volume reduction of individual fibroids in fibroid nucleation or hysterectomy.
- **Premenopausal breast cancer**
- **Treatment of central precocious puberty** (girls under 9 years of age, boys under 10 years of age).

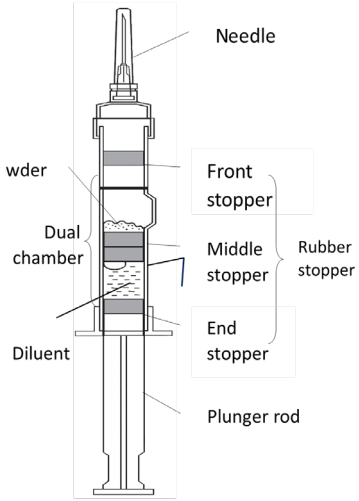
DOSAGE AND ADMINISTRATION

The lyophilized microcapsules of *ENANTONE L.P. 11.25 mg* are to be reconstituted and administered according to the following directions:

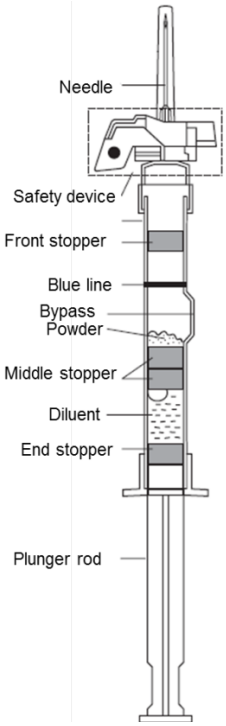
For vial and ampoule

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 EVERY THREE MONTHS**.

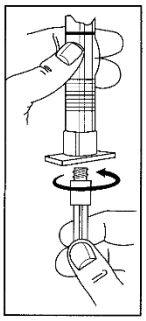
For Dual Chamber Pre-filled Syringe (DPS) with a needle;
For Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle
Powder and fluid must be mixed before use. Read and follow the instructions below.



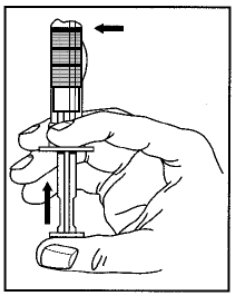
Dual Chamber Pre-filled Syringe (DPS) with a needle



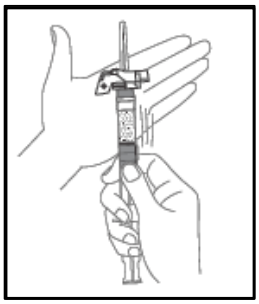
Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle



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.



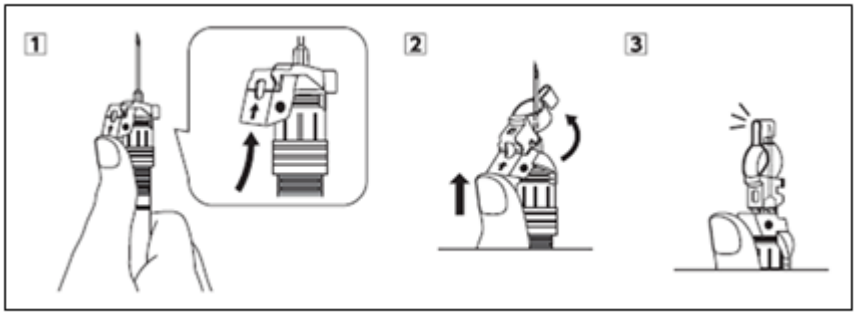
3. Tap gently on the syringe to ensure that there are no large quantities of powder remaining on the chamber wall.
4. Hold the syringe upright with the tip of the needle upwards. Push the plunger in slowly (approximately 6-8 seconds) until the front edge of the middle rubber stopper reaches the blue 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.



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. 11.25 mg* DPS must be mixed and used immediately.
10. The patient must be instructed not to massage the injection site.

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



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.
As with other drugs administered regularly by injection, the injection site should be varied periodically**.**

- **Treatment of Prostate Cancer**

After reconstitution, 11.25 mg of leuprorelin acetate (Enantone L.P. 11.25 mg) administered **ONCE EVERY THREE MONTHS** as a single **subcutaneous or intramuscular** injection.

The majority of patients will respond to this dosage. *ENANTONE L.P. 11.25 mg* therapy should not be discontinued when remission or improvement occurs.
Response to *ENANTONE L.P. 11.25 mg* therapy should be monitored by clinical parameters and by measuring prostate-specific antigen (PSA) serum levels. Clinical studies have shown that testosterone levels increased during the first 4 days of treatment in the majority of non-orchidectomised patients. They then decreased and reached castrate levels by 2-4 weeks. Once attained, castrate levels were maintained as long as drug therapy continued. If a patient's response appears to be sub-optimal, then it would be advisable to confirm that serum testosterone levels have reached or are remaining at castrate levels. Transient increases in acid phosphatase levels sometimes occur early in the treatment period but usually return to normal or near normal values by the 4th week of treatment.

Elderly men: as for adults

- **Treatment of Endometriosis and Uterine Fibroids**

Endometriosis: Usually, for adults, 11.25 mg of leuprorelin acetate (*ENANTONE L.P. 11.25 mg*) is **subcutaneously or intramuscularly** administered **ONCE EVERY THREE MONTHS** after reconstitution. However, when the patient's weight is less than 50 kg, the 1.88 mg preparation (*ENANTONE L.P. 1.88 mg*) may be used. Treatment should be started during the first five days of the menstrual cycle.

Monotherapy: *ENANTONE L.P. 11.25 mg* is indicated for management of endometriosis, including pain relief and reduction of endometriosis lesions, for up to 6 months.

Combination therapy: In two clinical studies, *3.75 mg* leuprorelin was administered monthly for a period of 12 months with concurrent hormonal replacement therapy (**norethindrone acetate 5 mg daily**) and calcium supplementation.
These studies demonstrated that concurrent hormonal therapy (norethindrone acetate 5 mg daily) was effective in significantly reducing the loss of bone mineral density loss that occurs with leuprorelin treatment, without comprising the efficacy of leuprorelin in relieving symptoms of endometriosis.

To flatten the endometrium before planned hysteroscopic operative interventions, an injection of *ENANTONE L.P. 11.25 mg* is administered s.c. or i.m. The success of treatment can be evaluated ultrasonically by measuring the endometrial thickness.

Uterine Fibroids: Usually, for adults, 1.88 mg of leuprorelin acetate (*ENANTONE L.P. 1.88 mg*) is **subcutaneously or intramuscularly** administered **once a month**. However, for patients with heavy weight or those with markedly enlarged uterus, 11.25 mg (*ENANTONE L.P. 11.25 mg*) is administered **ONCE EVERY THREE MONTHS**. The administration of this drug should be initiated on the first to fifth day after the start of menstrual period.

The duration of administration should be restricted to a period of 6 months. Repeated treatments should be carried out only after careful consideration of the risks and benefits by the treating physicians. This includes the measurement of bone density before the start of any treatment.

ENANTONE L.P. 11.25 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine fibroids. The clinician may wish to consider a one-month trial period on iron alone in as much as some of the patients will respond to iron alone.

- **Treatment with Premenopausal breast cancer**

Usually, for adults, 11.25 mg of Leuprorelin Acetate is **subcutaneously or intramuscular** administered once every 12 weeks (**ONCE EVERY THREE MONTHS**)

- **Paediatric population**

The treatment of children with leuprorelin acetate should be under the overall supervision of the paediatric endocrinologist.

The dosing scheme needs to be adapted individually.

11.25 mg of Leuprorelin Acetate is **subcutaneously or intramuscularly** administered once every 12 weeks (**ONCE EVERY THREE MONTHS**)

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 paediatrician 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.

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. 11.25 mg* may cause fetal harm when administered to a pregnant women.
4. Use in women who are breast feeding. Because of the lack of data regarding *ENANTONE L.P 11.25 mg* excretion in milk and its potential effects on nursing babies, *ENANTONE L.P. 11.25 mg* should not be used on nursing mother.
5. In girls with central precocious puberty:
   - Pregnancy and lactation
   - Undiagnosed vaginal bleeding.

SPECIAL WARNING AND SPECIAL PRECAUTIONS FOR USE

All patients, including central precocious puberty patients

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

- ***Depression***

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

- ***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.

Central precocious puberty patients

Before starting treatment with leuprorelin acetate in pubescent pediatric females, pregnancy must be excluded (See Contraindications).

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

Pseudotumor cerebri / idiopathic intracranial hypertension

Pseudotumor cerebri (PTC)/idiopathic intracranial hypertension has been reported in pediatric patients receiving leuprorelin acetate. Patients should be monitored for signs and

symptoms of PTC, including papilledema, headache, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea. If PTC is confirmed permanently discontinue use of leuprorelin acetate and treat the patient in accordance with the established treatment guidelines.

Adult patients only

- ***Metabolic changes and cardiovascular risk***

Inhibition of endogenous sex hormone production, such as during androgen deprivation therapy as identified from epidemiological data or 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 syndromes or cardiovascular diseases should be appropriately monitored

Prostate cancer patients only

- ***Flare phenomenon***

In the initial stages of therapy, a transient rise in levels of testosterone, dihydrotestosterone and acid phosphatase may occur. In some cases, this may be associated with a "flare" or exacerbation of the tumor growth resulting in temporary deterioration of the patient's condition. These symptoms usually subside on continuation of therapy.

"Flare" may manifest itself as systemic or neurological symptoms where the carcinoma has metastasized (e.g. to the spine), including bone pain, weakness of lower extremities and paresthesia in some cases. Urinary tract obstruction and hematuria may be observed as consequence of flare of the primary carcinoma.

In order to reduce the risk of flare, an anti-androgen may be administered beginning 3 days prior to leuprorelin therapy and continuing the sequelae of an initial rise in serum testosterone. If an anti-androgen is used over a prolonged period, due attention should be paid to the contraindications and precautions associated with its extended use.
Patients at risk of ureteric obstruction or spinal cord compression should be considered carefully and also be closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens. Should urological or neurological complications occur, these should be treated by appropriate specific measures.

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 with leuprorelin acetate.

- ***Bone Mineral Loss***

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss which, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture.

- ***QT prolongation***

Androgen deprivation therapy may prolong the QT interval.
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (See Interaction with other

medicaments and other forms of interaction) physicians should assess the risk and benefits of each medicinal product, including the potential for Torsade de pointes prior to initiating leuprorelin acetate.

Endometriosis, Uterine fibroids, Breast cancer patients only

1. Before starting treatment with *ENANTONE L.P. 11.25 mg*, pregnancy must be excluded (See Contraindications). During the period of the treatment, the patient should be instructed to prevent conception with the use of non-hormonal methods.
2. During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

3. *ENANTONE L.P. 11.25 mg* may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures.
4. Prior to administration of leuprorelin acetate, undiagnosed abnormal vaginal bleeding must be investigated, diagnosis confirmed and relevant management initiated.

5. Bone Mineral Loss

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.

The induced of hypo-estrogenic state results in a loss in bone density over the course of treatment, some of which may not be reversible. The extent of bone demineralization due to hypo-estrogenemia is proportional to time. The level of bone loss with GnRH analogues such as ENANTONE L.P. can be up to 5% after 1 year of treatment. During one e.g. six-month treatment period, this bone loss should not be significant.

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 corticosteriod, ENANTONE L.P. 11.25 mg therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with ENANTONE L.P. 11.25 mg is instituted. This is particularly important in women with uterine fibroids where age related bone loss have already begun to occur.

Endometriosis patients only

1. As monotherapy, the duration of administration of leuprorelin acetate should be limited to 6 months, as its use is associated with an increased risk of bone mineral loss If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed.

Uterine fibroid patients only

1. When considering the preoperative treatment of fibroids it is mandatory to confirm the diagnosis of fibroids and exclude an ovarian mass, either visually by laparoscopy or by ultrasonography or other investigative technique, as appropriate, before *ENANTONE L.P. 11.25 mg therapy* is instituted.
2. In women with submucous fibroids there have been reports of severe bleeding following the administration of *ENANTONE L.P. 11.25 mg* as a consequence of the acute degeneration of the fibroids. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required.
3. Before using *ENANTONE L.P. 11.25 mg* for the preoperative treatment of uterine fibroids, patients with major risk factors for decreased bone mineral contents (see above) should have their bone density measured and where results are below the normal (5^{th} percentile by DEXA scan) range, *ENANTONE L.P.* 11.25 mg therapy should not be started. The duration of administration of leuprorelin acetate should be limited to 6 months, as its use is associated with an increased risk of bone mineral loss. If it is necessary to resume administration of leuprorelin acetate, changes in bone parameters should be closely followed.

Premenopausal breast cancer

1. When starting treatment with *ENANTONE L.P. 11.25 mg*, absence/presence of hormone receptor expression should be confirmed as a rule. When hormone receptor expression is confirmed to be negative, *ENANTONE L.P. 11.25 mg* should not be used.
2. A decrease in bone mass may occur owing to estrogen reducing effect of *ENANTONE L.P. 11.25 mg*. 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.
3. In the early period after the first administration of *ENANTONE L.P. 11.25 mg*, a transient elevation of the serum level of estrogen may occur owing to the stimulating effect of *ENANTONE L.P. 11.25 mg*, as a highly active GnRH derivative, on the pituitary-gonad system, resulting in a transient aggravation of bone pain, etc. In such a case, symptomatic treatment should be given.
4. If antitumor effect is not obtained with *ENANTONE L.P. 11.25 mg* and any progression of the tumor is observed, the administration should be discontinued.

Precautions

Male: Patients with urinary obstruction and/or patients with metastatic vertebral lesions should begin *ENANTONE L.P. 11.25 mg* therapy under close supervision for the first few weeks of treatment and may have incidences of flare up syndrome.

Female: Since menstruation should stop with effective doses of *ENANTONE L.P. 11.25 mg,* the patients should notify her physician if regular menstruation persists.

All children with central precocious puberty:

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

The therapy is a long-term treatment, adjusted individually. *ENANTONE L.P. 11.25 mg* 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.

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.

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, oestradiol) should be monitored at 2-week intervals.

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.

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 GnRH 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.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

Prostate cancer patients only

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of leuprorelin acetate with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as Class IA (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin and antipsychotics, should be carefully evaluated (See Special warning and precautions for use).

PREGNANCY AND LACTATION

ENANTONE L.P. 11.25 mg should not be administered to pregnant females, females 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.]

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.

UNDESIRABLE EFFECTS

General (all indications)

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with pituitary adenoma.

Prostate cancer

Flare phenomenon:

Aggravation of the signs and symptoms of prostate cancer may occur following a transient increase in serum testosterone level in the early period after initiation of treatment, for example urinary tract obstruction and hematuria (as urinary symptoms). In patients with spinal cord compression due to metastasis to the spine, bone pain, weakness of lower extremities and paresthesia (as neurologic symptoms) may also occur.

Therefore, particular care should be taken in patients with metastasis to the spine and those with urinary tract obstruction. Careful observation should be made during the first several weeks after initiation of the treatment.

Blood and lymphatic system disorders:

Anemia, leucopenia, thrombocytopenia

Immune system disorders:

Hypersensitivity including anaphylactic reaction, rash and pruritus

Metabolism and nutrition disorders:

Decreased appetite, metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance), Weight increase

Psychiatric disorders:

Libido decreased, depression, mood changes, insomnia

Nervous system disorders:

Paresthesia, dizziness, headache, pituitary haemorrhage, seizure

Eye disorders:

Visual impairment

Cardiac disorders:
QT prolongation (See Special warnings and precautions for use and Interaction with other medications and other forms of interaction), palpitations

Vascular disorders:
Hot flush

Gastrointestinal disorders:
Nausea, Vomiting, Diarrhea

Hepatobiliary disorders:
Liver function test abnormal, usually transient, liver function abnormal (including jaundice)

Skin and subcutaneous tissue disorders:
Hyperhidrosis

Respiratory thoracic and mediastinal disorders:
Interstitial lung disease

Musculoskeletal and connective tissue disorders:
Bone pain, bone density decreased, muscular weakness, osteoporosis (including vertebral body fractures), arthralgia, myalgia

Renal and urinary disorders:
Urinary tract obstruction

Reproductive system and breast disorders:
Erectile dysfunction, testicular atrophy, gynaecomastia

General disorders and administration site conditions:
Injection site reaction, edema, fatigue

Endometriosis, uterine fibroids
Blood and lymphatic system disorders:
Anemia, leucopenia, thrombocytopenia

Immune system disorders:
Hypersensitivity, including anaphylactic reaction, rash and pruritus

Metabolism and nutrition disorders:
Weight fluctuation, decreased appetite, metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)

Psychiatric disorders:
Libido decreased, affect lability, depression, sleep disorder

Nervous system disorders:
Headache, dizziness, paresthesia, pituitary haemorrhage, seizure

Eye disorders:

Visual impairment

Cardiac disorders:
Palpitations

Vascular disorders:
Hot flush

Gastrointestinal disorders:

Nausea, vomiting, diarrhea

Hepatobiliary disorders:
Liver function test abnormal, usually transient, liver function abnormal (including jaundice)

Skin and subcutaneous tissue disorders:
Alopecia, hyperhidrosis

Respiratory thoracic and mediastinal disorders:
Interstitial lung disease

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia, bone mineral density loss, 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

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 were feeling of warmth/ hot flushes /feeling of hot flushes/ 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 *ENANTONE L.P.* 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, and 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 were hot flushes in 245 patients, weight increase in 234 patients, and excessive sweating in 228 patients, etc.

Adverse reactions, including abnormalities in laboratory data, were observed in 121 (19.1%) of 635 patients in the post-marketing investigation of the results of drug use (as of the end of the reexamination period). Major adverse reactions were disorder in the injection site (injection site induration in 40 patients, injection site pain in 17 patients, injection site erythema in 15 patients, injection site swelling in 10 patients), and hot flushes in 35 patients, etc.

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

Other adverse reactions

	≥5%	0.1% - < 5%	< 0.1%	Frequency Unknown**
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 discharge, 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	Myalgia	Osteoporosis (including vertebral body fractures), muscular weakness
4) **Dermatologic**		Acne, dry skin, alopecia, hypertrichosis or nail abnormality		
5) **Psychoneurologic**		Sleepiness, irritated feeling, hypomnesia, decreased attentiveness or paresthesia	Pituitary hemorrhage	

	≥5%	0.1% - < 5%	< 0.1%	Frequency Unknown**
6) Hypersensitivity		Rash or pruritus		Anaphylactic reaction
7) **Hepatic***		Increased AST(GOT), ALT(GPT), ALP, LDH, γ-GTP or bilirubin	Liver function abnormal (including jaundice)	
8) Gastrointesti-nal		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***	Induration	Pain and redness		Reactions at the injection site such as abscess, swelling, ulcer, pruritus, granuloma, mass, warmth and necrosis

	≥5%	0.1% - < 5%	< 0.1%	Frequency Unknown**
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, visual impairment	Weight decrease, taste abnormality or abnormal thyroid function	Seizures, *metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance), interstitial lung disease

* Close observation should be made

** Frequency is unknown because these were from spontaneous reports.

In Children

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, depression

Nervous system disorders:

Common: Headache

Uncommon: Pseudotumor cerebri / idiopathic intracranial hypertension

Very rare: Pituitary haemorrhage

Frequency not known: Seizure

Gastrointestinal disorders:

Common: Abdominal pain / abdominal cramps, nausea, vomiting

Skin and subcutaneous tissue disorders:

Common: Acne

Musculoskeletal and connective tissue disorders:

Not known: Myalgia

Reproductive system and breast disorders:

Common: Vaginal hemorrhage, spotting, vaginal 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 under dosage. The pituitary suppression should then be determined by an LHRH test.

General disorders and administration site conditions:

Common: injection site reactions

OVERDOSE

There is no clinical experience with the effects of an acute overdose of leuprorelin acetate. In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnea, decreased activity and local irritation at the injection sites. In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive.

CLINICAL STUDIES

Prostate cancer

A randomised, open-label, comparative multi-centre study was performed to compare the efficacy and safety of the 3.75mg and 11.25mg depots of leuprorelin. 48% of patients included had locally advanced disease (T3N0M0), 52% of patients had metastatic disease. Mean serum testosterone level fell below the threshold for chemical castration (0.5 ng/ml) at one month of treatment, continuing to decrease thereafter and stabilising at a value below the castration threshold. The decline in serum PSA mirrored that of serum testosterone in both groups.

In an open, prospective clinical trial involving 205 patients receiving 3.75mg leuprorelin on a monthly basis as treatment for metastatic prostate cancer, the long-term efficacy and safety of leuprorelin was assessed. Testosterone levels were maintained below the castrate threshold over the 63-month follow up period. Median survival time exceeded 42.5 months for those receiving monotherapy and 30.9 months for those receiving leuprorelin in combination with anti-androgens (this difference relating to baseline differences between groups)

In a meta-analysis involving primarily patients with metastatic disease, no statistically significant difference in survival was found for patients treated with GnRH analogues compared with patients treated with orchidectomy.

In another randomised, open-label, multi-centre comparative trial, leuprorelin in combination with flutamide has been shown to significantly improve disease-free survival and overall survival when used as an adjuvant therapy to radiotherapy in 88 patients with high-risk localised (T1-T2 and PSA of at least 10 ng/mL or a Gleason score of at least 7), or locally advanced (T3-T4) prostate cancer. The optimum duration of adjuvant therapy has not been established. This US study used a higher dose of leuprorelin (7.5 mg/month) which is therapeutically equivalent to the European licensed dose.

The use of a GnRH agonist may be considered after prostatectomy in selected patients considered at high risk of disease progression. There are no disease-free survival data or survival data with leuprorelin in this setting.

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	Administrative/ observation period	Antitumor effect (effectiveness rate) *	Inhibition rate of menopausal level **
Premenopausal advanced/recurrent breast cancer cases	Twice	24 weeks	22.7% (5 cases/22 cases)	-
Post (premenopausal breast cancer) surgery cases	Twice	24 weeks	-	98.4% (61 cases/62 cases)

* 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)
** 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 70 of the above patients in status of post (premenopausal breast cancer) surgery was 93.5% (two-sided 95% confidence interval: 87.23 to 99.74%).

In a randomized controlled, non-inferiority design study conducted in Germany and the Ukraine in which Leuprorelin Acetate 11.25 mg at 3-month intervals or cyclophosphamide, methotrexate, fluorouracil (CMF) therapy was given to pre- and peri-menopausal women with breast cancer (T1-3, N+M0), positive estrogen receptor status (ER+) and curative approach of surgery within six weeks prior to enrolment progression-free survival rates were shown as follows.

Drugs	Dosage and administration	Progression-free survival rate 2 years after start of treatment (primary endpoint)	Progression-free survival rate 5 years after start of treatment
Leuprorelin Acetate 11.25 mg	subcutaneous injection at 3-month intervals for 24 months	83.0% (224/270 cases) (95%CI 77.9 – 87.2)	60.5% (95%CI 54.2 – 66.5)
CMF therapy cyclophosphamide 500mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2	1 cycle [each drug given intravenously twice monthly (on the 1st and 8th days)] x 6 times (6 months)	80.9% (207/256 cases) (95%CI 75.5 – 85.5)	60.6% (95%CI 54.1 – 66.8)

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

ENANTONE L.P. 11.25 mg 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 in 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.

ENANTONE L.P. 11.25mg is inactive when given orally.

In children:

Reversible suppression of pituitary gonadotropin release occurs, with a subsequent decrease in oestradiol (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;
- Arrest/involution of somatic pubertal development (Tanner stages);

- Improvement/normalisation 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 15 mg 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.

Pharmacokinetic Properties

Leuprorelin actetate is well absorbed after subcutaneous injection. It binds to the luteinising hormone releasing hormone (LHRH) receptors and is rapidly degraded. An initially high plasma level of leuprorelin peaks at around 3 hours after *ENANTONE L.P. 11.25 mg* injection, followed by a decrease to maintenance levels in 7 to 14 days. *ENANTONE L.P. 11.25 mg* provides continuous plasma levels for up to 117 days resulting in suppression of testosterone to below castration level within 4 weeks of the first injection in the majority of patients.

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

<u>In children</u>:

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).

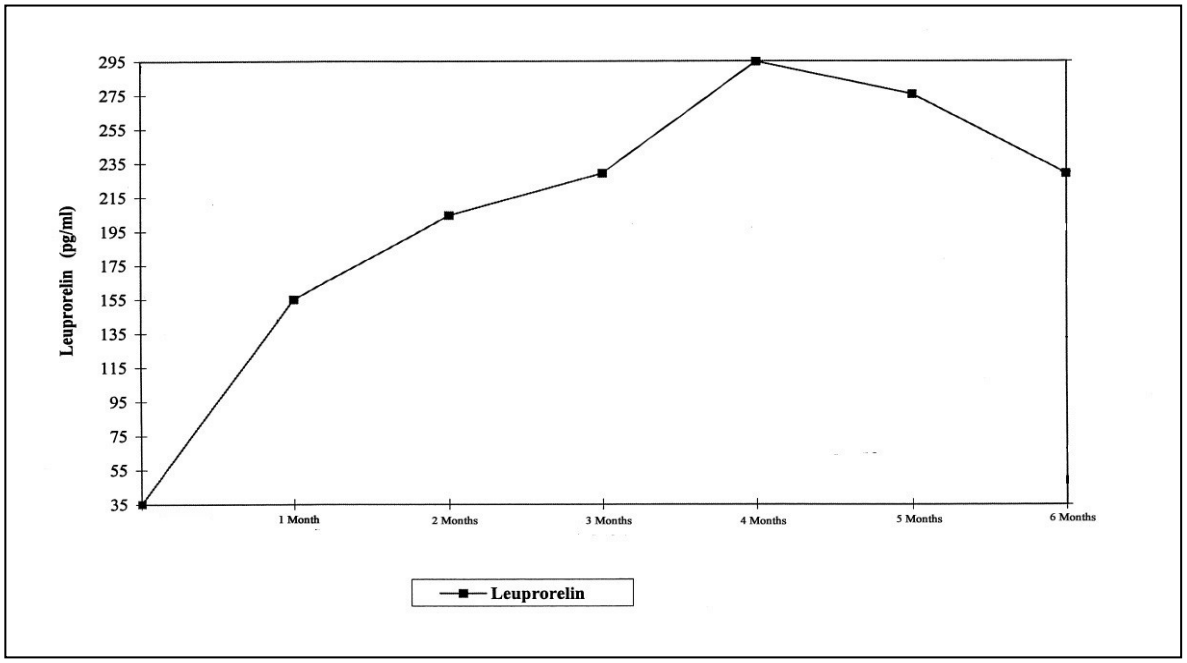
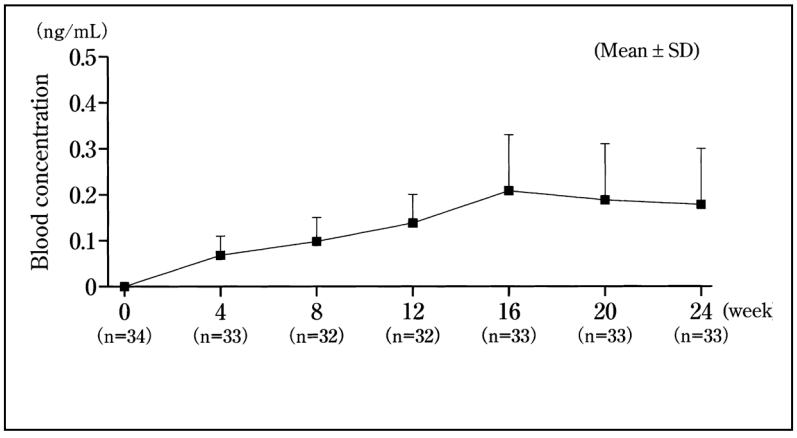


Figure 1: Leuprorelin serum levels during the first six months of treatment with the leuprorelin acetate 3-month depot formulation (two s.c. injections) (n=42-43)

Premenopausal breast cancer

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 of leuprorelin including its metabolite M1 attained steady state at week 16 after administration, and remained at approximately 0.2 ng/mL up to week 24.



Preclinical Safety Data

Animal studies have shown that leuprorelin acetate has 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 studied showed increased fetal mortality and decreased fetal weights reflecting the pharmacological effects of this GnRH agonist.

INCOMPATIBILITIES

No other fluid other than the sterile vehicle provided for *ENANTONE L.P. 11.25 mg* can be used for the reconstitution of *ENANTONE L.P. 11.25 mg* powder.

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.

PACKAGE

Vial with powder and ampule with 2 ml vehicle.
Dual chamber pre-filled syringe (DPS) with a needle (23 G)

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

Manufactured by

Takeda Pharmaceutical Company Limited, Hikari Plant
Yamaguchi, Japan
Or
Takeda Pharmaceutical Company Limited, Osaka Plant
Osaka, Japan
PACKED BY
Takeda Pharmaceutical Company Limited, Hikari Plant
Yamaguchi, Japan

Imported by

Takeda (Thailand), Ltd.
Bangkok, Thailand

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