ENANTONE L.P. 3.75 MG

(LEUPRORELIN ACETATE FOR SUSTAINED RELEASE SUSPENSION)

ENANTONE L.P. 3.75 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 3.75 mg leuprorelin acetate as lyophilized microcapsules.
Each ampule contains 2ml sterile vehicle which is used to reconstitute *ENANTONE L.P. 3.75 mg* powder for administration to the patient.

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

Each DPS contains 3.75 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 localized 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 extragenital localization (From stage I to stage IV)
- Uterine Fibroids (Leiomyomata)
- Central precocious puberty (CPP)
- Premenopausal breast cancer

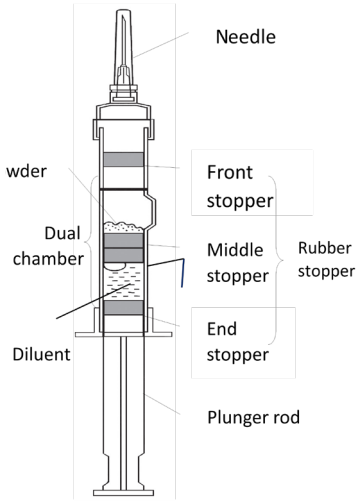
DOSAGE AND ADMINISTRATION

The lyophilized microcapsules of *ENANTONE L.P. 3.75 mg* are to be reconstituted and administered with the following directions:

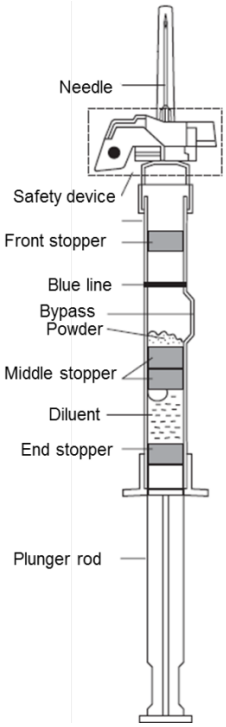
For vial and ampule

1. Using a syringe with a 23 gauge needle, withdraw 2 ml of diluent from the 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 **subcutaneously or intramuscularly** at the time of reconstitution.

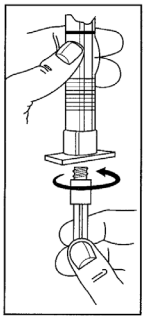
For Dual Chamber Pre-filled Syringe (DPS) with a needle;
For Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle
Powder and fluid must be mixed before use. Read and follow the instructions below.



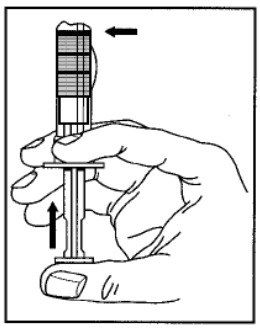
Dual Chamber Pre-filled Syringe (DPS) with a needle



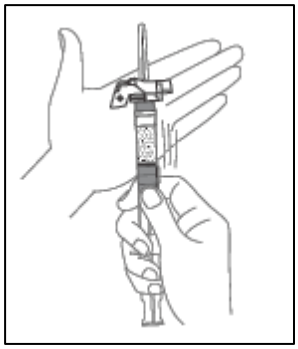
Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with a needle



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.

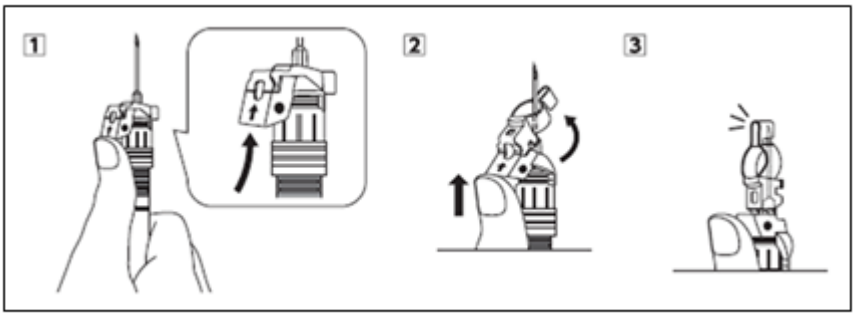


3. Tap gently on the syringe to ensure that there are no large quantities of powder remaining on the chamber wall.
4. Hold the syringe <u>upright</u> with the tip of the needle upwards. Push the plunger in slowly (approximately 6-8 seconds) until the front edge of the middle rubber stopper reaches the 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. 3.75 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 use immediately. As with other drugs administered by injection, the injection site should be varied periodically.

- **Treatment with Prostate cancer**

After reconstitution, 3.75 mg of leuprorelin acetate (*ENANTONE L.P. 3.75 mg*) is administered **once a month** as a single **subcutaneous or intramuscular injection**.

The majority of patients will respond to a 3.75 mg dose. *ENANTONE* therapy should not be discontinued when remission or improvement occurs. Response to *ENANTONE L.P. 3.75 mg* therapy may be monitored by clinical parameters and by measuring serum levels of testosterone and acid phosphatase. 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. 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.

- **Treatment with Endometriosis, Uterine Fibroids and Premenopausal breast cancer**

Endometriosis: Usually, for adults, 3.75 mg of leuprorelin acetate (*ENANTONE L.P. 3.75 mg*) is **subcutaneously or intramuscularly** administered **once a month** after reconstitution. However, when the patient's weight is less than 50 kg, 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. 3.75 mg* is indicated for management of endometriosis, including pain relief and reduction of endometriosis lesions, for up to six 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.

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, 3.75 mg (*ENANTONE L.P. 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.

Recommended duration of therapy with *ENANTONE L.P. 3.75 mg* is up to 3 months. The symptoms associated with uterine fibroids will recur following discontinuation of therapy. If additional treatment with *ENANTONE L.P. 3.75 mg* is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

Premenopausal breast cancer: After reconstitution, 3.75 mg of leuprorelin acetate (*ENANTONE L.P. 3.75 mg*) is administered **once a month** as a single **subcutaneous or intramuscular** injection. Bone density should be assessed prior to initiation of therapy and during therapy to ensure that values are within normal limits.

- **Treatment with central precocious puberty**.

Administer 90-400 μg/kg of leuprorelin acetate **subcutaneously or intramuscularly once a month**. The dose may be adjusted according to the patient's response.

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 females who are or may become pregnant while receiving the drug as *ENANTONE L.P. 3.75 mg* may cause fetal harm when administered to pregnant females.

4. Use in females who are breast feeding. Because of the lack of data regarding *ENANTONE L.P 3.75 mg* excretion in milk and its potential effects on nursing babies, *ENANTONE L.P. 3.75 mg* should not be used on nursing mother.

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 careful individual appraisal of the risks and benefits.

Bone mineral density (BMD) may decrease during GnRH analogue therapy in children with 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.

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 change or syndrome, or cardiovascular diseases should be appropriately monitored.

Diabetic patients may require more frequent monitoring of blood glucose during treatment with *ENANTONE L.P. 3.75 mg*.

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 for the first two to three weeks of treatment. This has been reported to prevent 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 risks 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. 3.75 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. 3.75 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 generally accepted level of bone loss with GnRH analogues such as *ENANTONE L.P. 3.75 mg* is 5%. During e.g. one six-month treatment period, this bone loss should not be important.

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. 3.75 mg* therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with *ENANTONE L.P. 3.75 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. Leuprorelin acetate can however be administered for a period of up to 12 months with concurrent hormonal replacement therapy (norethindrone acetate 5 mg daily). 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. 3.75 mg* therapy is instituted.
2. 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.

Precaution

Male:

Patients with urinary obstruction and/or patients with metastatic vertebral lesions should begin *ENANTONE L.P. 3.75 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. 3.75 mg,* the patients should notify her physician if regular menstruation persists.

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. 3.75 mg should not be administered to pregnant females or nursing mothers (See Contraindications).

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, breast cancer
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, bone pain

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

Central precocious puberty
In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

The following convention is used (where available) for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to< 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Immune system disorders:
Very rare: Hypersensitivity, anaphylactic reaction

Psychiatric disorders:
Common: Affect 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, nausea, vomiting

Skin and subcutaneous tissue disorders:
Common: Acne

Musculoskeletal and connective tissue disorders:

Not known: Myalgia

Reproductive system and breast disorders:
Common: Vaginal haemorrhage, 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 reaction

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

A randomised, open-label, comparative multi-centre study in patients with prostate cancer was performed to compare the efficacy and safety of the 3.75 mg and 11.25 mg 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 prostate cancer patients primarily 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, in prostate cancer patients 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 (7.5mg/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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Enantone LP 3.75mg 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.

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 15mg monthly for > 4 years resumption of pubertal progression were observed after cessation of treatment. Follow up of 20 female subjects to adulthood showed normal menstrual cycles in 80% and 12 pregnancies in 7 of the 20 subjects including multiple pregnancies for 4 subjects

Pharmacokinetic Properties

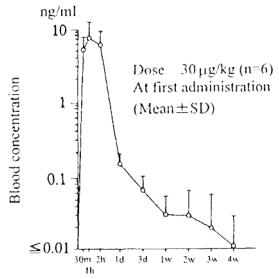
Studies show that single intramuscular or subcutaneous doses of leuprorelin acetate over the dose range 3.75 to 15 mg results in detectable levels of leuprorelin acetate for more than 28 days, good bioavailability, a consistent and predictable pharmacokinetic profile, and biological efficacy at plasma 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

Children with Central Precocious Puberty (CPP)

Following a single subcutaneous administration of leuprorelin acetate 1 month depot at a dosage of 30 mcg/kg body-weight, peak serum levels of 7.81 ± 3.59 ng/mL were attained at about 1 hour after administration. Serum levels declined rapidly to 0.15 ± 0.06 ng/mL by day 1 after administration and remained below 0.07 ng/mL from day 3 for 4 weeks (Figure 1). The AUC 0-672 was 105.78 ± 52.40 ng.hr/mL.

Figure 1. Plasma concentrations of leuprorelin acetate in children



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

CAUTIONS FOR STORAGE

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

PACKAGING

Vial with powder and ampule with 2 ml 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.
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