ENANTONE L.P. 30 mg

Leuprorelin Acetate 6 Month Depot Injection

ENANTONE L.P. 30 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 6 month depot injection.

COMPOSITION

Each Dual Chamber Pre-filled Syringe (DPS) contains 30.0 mg leuprorelin acetate and 1 ml sterile vehicle with a needle (23G).

The DPS is a dual chamber syringe with white powder in the front chamber and clear, colorless fluid in the rear chamber.

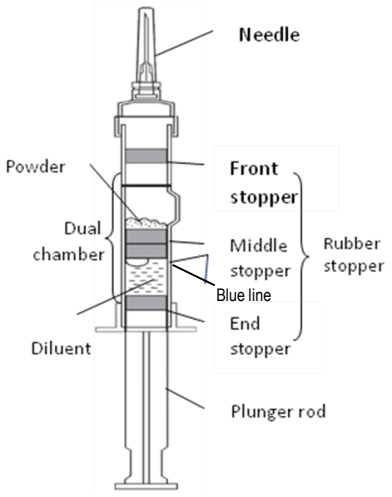
INDICATION

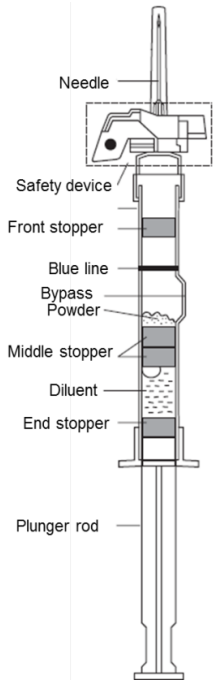
Advanced Prostate Cancer

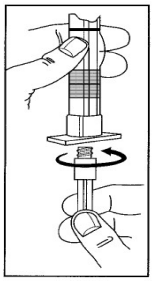
DOSAGE AND ADMINISTRATION

ENANTONE L.P. 30 MG DPS containing 30.0 mg leuprorelin acetate suspended in 1 ml sterile vehicle are administered subcutaneously or intramuscularly **once every six months**

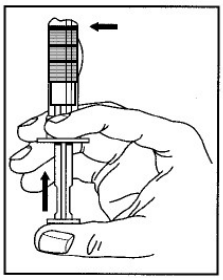
For Dual Chamber Pre-filled Syringe (DPS) with needle;
For Dual Chamber Pre-filled Syringe and Safety Device (DPS-SD) with needle
Powder and fluid must be mixed afresh each time before use. Read and follow the instructions below.



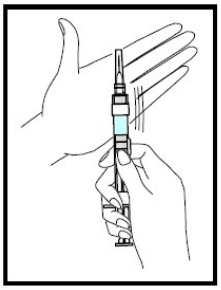




1. To prepare for an injection, screw the plunger rod into the end stopper of the syringe.
2. Ensure that the needle is properly fastened to the syringe.
   NOTE: Never pull back the plunger rod during the following process.

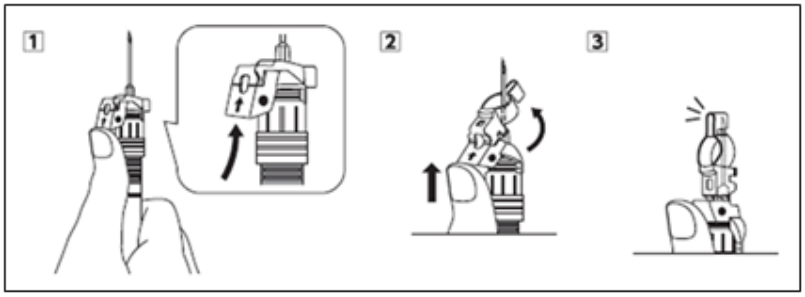


3. Tap gently on the syringe to ensure that there are no large quantities of powder remaining on the chamber wall.
4. Hold the syringe <u>upright</u> with the tip of the needle upwards. Push the plunger in slowly (approximately 6-8 seconds) until the front edge of the middle rubber stopper reaches the 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 <u>upright</u>. 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 bubble.
7. Hold the syringe <u>upright</u>. With the other hand, pull the needle cap upwards without twisting.
8. Hold the syringe <u>upright</u>. 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. 30 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 with Advanced Prostate Cancer

After reconstitution, one DPS administered **ONCE EVERY SIX MONTHS** as a single **subcutaneous or intramuscular** injection. The application interval should be 168 days to maximum 182 days (24 to 26 weeks).

The injection site should be changed every six months. Injection sites may include abdominal skin, buttocks, and upper thigh.

Generally, the treatment of advanced prostate cancer with *ENANTONE L.P. 30 mg* is continued on a long-term basis.

Treatment with *ENANTONE L.P. 30 mg* should be monitored for success on a regular basis by means of clinical examinations as well as laboratory evaluations of prostate-specific antigen (PSA), and serum testosterone levels, especially in case of potential clinical signs of progression presenting despite adequate treatment.

Note: As animal experimental findings demonstrated, it is crucial to avoid accidental intra-arterial injection, in view of the potential onset of thrombosis of small vessels distal to the injection site.

CONTRAINDICATIONS

Patients with a history of hypersensitivity to the ingredients of the preparation or synthetic LH-RH or LH-RH derivatives.

SPECIAL WARNING AND SPECIAL PRECAUTIONS FOR USE

General

Diabetic patients may require more frequent monitoring of blood glucose during treatment with *ENANTONE L.P. 30 mg.*

Response to treatment with *ENANTONE L.P. 30 mg* can be monitored by measurement of serum levels of testosterone and PSA (prostate-specific antigen).

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

ENANTONE L.P. 30 mg contains less than 1 mmol sodium (23 mg) per one dual chamber prefilled syringe. Presently, there is no experience available regarding treatment in children.

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.

In case hormone-independence of the carcinoma has been demonstrated, treatment with *Enantone L.P. 30 mg.* is not indicated.

After surgical castration, treatment with *Enantone L.P. 30 mg.* does not lead to further reduction of testosterone levels.

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.

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: bone pain, urinary tract obstruction and hematuria (as urinary symptoms), weakness of lower extremities and paresthesia (as neurologic symptoms).

Particular care should be taken of patients having spinal cord compression due to metastasis to the spine, and those with urinary tract obstruction. In administration to such patients, careful observation should be made during the first several weeks after initiation of the treatment.

The adjuvant administration of a suitable anti-androgen is to be considered in the initial phase of therapy to alleviate the symptoms potentially associated with the initial increase in testosterone levels and to attenuate the exacerbated clinical symptoms.

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.

However, the development of osteoporosis due to hypogonadism is secondary to an increase in cortisol levels, and is more pronounced after orchiectomy than after administration of GnRH analogues. In patients at risk, the additional administration of a bisphosphonate may represent a prophylactic measure against such bone demineralization.

Metabolic changes and cardiovascular risk:
Epidemiological data have shown that during androgen deprivation therapy changes in the metabolic condition (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular diseases may occur. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be appropriately monitored.

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 Drug interaction) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating leuprorelin acetate.

DRUG INTERACTION

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, antipsychotics, should be carefully evaluated (see Special warning and precautions for use).

PREGNANCY AND LACTATION

ENANTONE L.P. 30 mg is not intended for the use in females and is generally contraindicated during pregnancy and lactation.

Fertility in men: Clinical and pharmacological studies in men showed that the depression of fertility was completely reversible 24 weeks at the latest after discontinuation of continuous leuprorelin acetate application.

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 DRUG REACTIONS

General
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:

Bone pain, Urinary tract obstruction (as urinary symptoms), Weakness of lower extremity, Paresthesia (as neurologic symptoms)

Immune system disorders:
Hypersensitivity including Anaphylactic reaction, Rash and Pruritus

Metabolism and nutrition disorders:
Decreased appetite

Psychiatric disorders:
Libido decreased, Depression

Nervous system disorders:
Paresthesia, Dizziness, Headache, Pituitary Haemorrhage, Seizure

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

Vascular disorders:
Hot flush

Gastrointestinal disorders:
Nausea, Vomiting, Diarrhea

Hepatobiliary disorders:
Liver function test abnormal, usually transient

Skin and subcutaneous tissue disorders:
Hyperhydrosis

Musculoskeletal and connective tissue disorders:
Bone pain, Bone density decreased, Muscular weakness

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, Oedema

OVERDOSE

To date, no symptoms of intoxication have been reported.
Even when administered in daily doses of up to 20 mg for a period of two years, like applied in the first clinical studies, no new side effects or side effects different from those observed with a daily dose of 1 mg or with a dose of 30mg administered every 6 months have been reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Pharmacotherapeutic group: Antineoplastics – Endocrine Therapy – GnRH analogues

ATC-code: L02AE02
Leuprorelin acetate, the active ingredient in *ENANTONE L.P. 30 mg*, is a synthetic analogue of the naturally occurring hypothalamic releasing factor, LHRH, which works to control the release of the gonadotropic hormones LH (luteinizing hormone) and FSH (follicle-stimulating hormone) from the anterior lobe of the pituitary gland. These hormones stimulate the gonadal steroid synthesis.

In contrast to the physiological LHRH released from the hypothalamus in a pulsatile mode, leuprorelin acetate, also known as an LHRH agonist, works to block the LHRH receptors of the pituitary gland with chronic therapeutic use, and after an initial short-term stimulatory effect, causes them to become “desensitized” (“down-regulated”).

As a consequence, reversible pituitary suppression of gonadotropin release occurs, followed by a decrease in testosterone levels, thereby influencing the growth of prostate cancer, which is normally stimulated by dihydrotestosterone (DHT) formed by reduction of testosterone in the prostate cells.

Chronic administration of leuprorelin acetate leads to a decrease in the number and/or sensitivity (“down-regulation”) of the LHRH receptors present in the pituitary gland, resulting in a decrease in LH, FSH, and DHT levels, thereby reducing the testosterone level to the castration range.

The hormone-decreasing and inhibitory effect of leuprorelin acetate on the growth of prostate cancer has also been demonstrated in animal studies.

Experimental and clinical studies demonstrated that 6-monthly treatment with *ENANTONE L.P. 30 mg* results in the inhibition of gonadotropin release after an initial stimulatory effect.

In the man the subcutaneous administration of *ENANTONE L.P. 30 mg* causes an initial short-term rise in LH and FSH, accompanied by a transient increase in testosterone and DHT levels. As a short term exacerbation of symptoms has been reported in the first few weeks of treatment in isolated cases, the administration of an appropriate anti-androgen should be considered in patients with prostate cancer.

Long-term administration of *ENANTONE L.P. 30 mg* leads to a decrease in LH and FSH levels in all patients, thereby resulting in a decrease in androgen in these patients to levels comparable to those seen after bilateral orchiectomy. These changes usually occur two to three weeks after commencement of therapy, and are maintained during the entire course of treatment. If appropriate, a treatment with *ENANTONE L.P. 30 mg*, which has to be administered every six months, represents a viable alternative to orchiectomy. To date, the maintenance of suppressed testosterone levels in the castration range with continuous administration of leuprorelin acetate has been confirmed for five years.

Pharmacokinetic Properties
The active ingredient leuprorelin acetate is continuously released from the lactic acid polymer for a period of 6 months after injection of the *ENANTONE L.P. 30 mg* depot suspension. The carrier polymer is absorbed over time in a similar fashion to surgical suture material.

After single s.c. injection of *ENANTONE L.P. 30 mg* serum levels of leuprorelin rise quickly with a subsequent decrease to a plateau within a few days. Within two hours

mean maximum serum levels of 102 ng/ml are measured. In the plateau phase detectable serum levels were found until up to > 26 weeks after administration. In some patients, leuprorelin levels have been observed for up to 30 weeks. Fig. 1 shows the course of leuprorelin levels after a single administration of *ENANTONE L.P. 30 mg*

An initial re-increase of testosterone levels was observed in median after approx. 200 days in case no subsequent injection was administered.

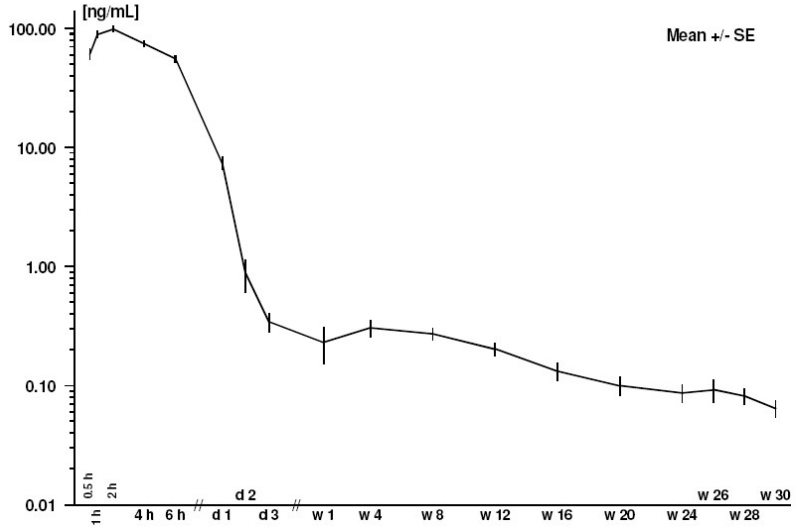


Fig. 1: Leuprorelin serum levels after a single s.c. administration of 30.0 mg leuprorelin acteate as *ENANTONE L.P. 30mg*.

The distribution volume of leuprorelin is 36 l in men; total clearance is 139.6 ml/min (measured under treatment with Enantone Monthly Depot).

With repeated administration, a persistent suppression of testosterone levels to the castration range occurs, without the testosterone levels undergoing a transient rise, as after the first injection.

In patients with impaired renal function, higher leuprorelin serum levels were measured in some cases whereas in patients with hepatic dysfunction lower values were found. However, this observation appears to be of no clinical relevance.

Preclinical Safety Data
Preclinical studies with leuprorelin acetate show impact on the reproductive system in both sexes, which are expected as a result of the known pharmacological effect. These effects are in principle reversible after a recovery phase (see Pharmacodynamic properties)

Leuprorelin acetate shows no teratogenic effect. Due to the pharmacological effect on the reproductive system embryotoxicity and – lethality appeared in rabbits.

Carcinogenicity studies have been performed in rats and mice over 24 months. After

subcutaneous injection a dose-dependent increase in pituitary adenomas at dosages of 0.6 mg to 4 mg/kg/day was observed in rats. No such effect was observed in mice, so that the effect in rats can be considered as species-specific.

Leuprorelin acetate had no mutagenic effect in a series of in vitro and in vivo studies.

INCOMPATIBILITIES

No other fluid other than the sterile vehicle provided for *ENANTONE L.P. 30 mg* can be used for the reconstitution of *ENANTONE L.P. 30 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

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
Osaka, Japan

Packed and Released by
Takeda Pharmaceutical Company Limited
Hikari-city, Yamaguchi, Japan

Imported by
Takeda (Thailand), Ltd.
Bangkok, Thailand

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