SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ENANTONE L.P. 11.25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- **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).

4.2 Posology and method of administration

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.

4.3 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

4.4 Special warnings and precautions for use

Use immediately after mixing as the suspension settle out very quickly following reconstitution.

<u>All patients, including central precocious puberty patients</u>

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.

• Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which can be life-threatening or fatal, have been rarely reported with leuprorelin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for delayed hypersensitivity reactions. If signs and symptoms suggestive of these reactions appear, leuprorelin should be withdrawn immediately and an alternative treatment considered (as appropriate).

<u>Central precocious puberty patients</u>

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.

<u>Endometriosis patients only</u>

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.

<u>Uterine fibroid patients only</u>

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 (5th 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.

4.5 Interaction with other medicinal products and other forms of 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 and antipsychotics, should be carefully evaluated (See Special warning and precautions for use).

4.6 Pregnancy, Lactation and Fertility

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.]

4.7 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.

4.8 Undesirable effects

The following convention is used 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).

All Patient Populations

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Metabolic disorders						Hepatic Steatosis
Psychiatric disorders		Depression, mood changes (long term use of leuprorelin)	Mood changes (short term use of leuprorelin)			
Nervous system disorders					Pituitary apoplexy (following initial administration in patients with pituitary adenoma), pituitary hemorrhage	Seizure
Skin and subcutaneous						Stevens-Johnson

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
tissue disorders						Syndrome, Toxic Epidermal Necrolysis, Erythema multiforme, Bullous dermatitis, Exfoliative dermatitis, Acute generalized exanthematous pustulosis, Toxic skin eruption

All Adult Populations

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Blood and lymphatic system disorders						Anemia, leucopenia, thrombocytopenia
Immune system disorders						Hypersensitivity, including anaphylactic reaction, rash, pruritus, urticaria, wheezing, fever and chills
Metabolism and nutrition disorders						Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Vascular disorders	Hot flush					
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Musculoskeletal and connective tissue disorders		Arthralgia	Myalgia			Bone mineral density loss, osteoporosis (including vertebral body fractures)
General disorders and administration site conditions		Edema				

Adult Females

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Nervous system disorders	Headache	Dizziness, paresthesia				
Hepatobiliary disorders			Hepatic function test abnormal, usually transient			Hepatic function abnormal (including jaundice)
Reproductive system and breast disorders		Breast tenderness				
General disorders and administration site conditions		Injection site reaction (e.g induration, erythema, pain, abscess, swelling nodules and necrosis				

Additional ADRs in Breast Cancer Patients or at Differing Frequency

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Metabolism and nutrition disorders	Weight increase, decreased appetite					
Psychiatric disorders		Insomnia				
Eye disorders		Visual impairment				
Cardiac disorders		Palpitations				
Gastrointestinal disorders	Nausea	Vomiting, diarrhea				
Skin and subcutaneous tissue disorders	Hyperhidrosis	Alopecia				
Musculoskeletal and connective tissue disorders	Bone pain, muscular weakness					
Reproductive	Vaginal	Vulvovaginitis				

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
system and breast disorders	hemorrhage, libido decreased, vulvovaginal dryness					
General disorders and administration site conditions	Fatigue					

Additional ADRs in Endometriosis/Uterine Fibroids Patients or at Differing Frequency

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Metabolism and nutrition disorders		Weight increase	Decreased appetite			
Psychiatric	Insomnia					

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
disorders						
Eye disorders			Visual impairment			
Cardiac disorders			Palpitations			
Gastrointestinal disorders		Nausea	Vomiting, diarrhea			
Skin and subcutaneous tissue disorders		Hyperhidrosis	Alopecia			
Musculoskeletal and connective tissue disorders		Muscular weakness				
Reproductive system and breast disorders		Breast atrophy, vulvovaginal dryness				Vulvovaginitis, vaginal hemorrhage, libido decreased
General disorders and administration			Fatigue			

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
site conditions						

Adult Males

In the initial phase of therapy, a short-term increase, also known as a flare-up, of the sex hormone level occurs (flare phenomenon). Adverse events, which may occur particularly at the beginning of treatment, include urinary tract obstruction (as urinary symptoms); In patients with spinal cord compression, bone pain, weakness of lower extremities and paresthesia (as neurologic symptoms) may also occur (see Special Warnings and Special Precautions for Use, 4.4)

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Metabolism and nutrition disorders	Weight increase	Decreased appetite				
Psychiatric disorders		Insomnia				
Nervous system disorders		Headache	Dizziness			

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Eye disorders						Visual impairment
Cardiac disorders						Palpitations, QT prolongation (see Special Warnings and Special Precautions for Use, 4.4 and Interaction with Other Medications and Other Forms of Interaction, 4.5)
Gastrointestinal		Nausea	Vomiting,			

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
disorders			diarrhea			
Hepatobiliary disorders		Hepatic function abnormal (including jaundice), Hepatic function test abnormal, usually transient				
Skin and subcutaneous tissue disorders	Hyperhidrosis					
Musculoskeletal and connective tissue disorders	Muscular weakness					
Reproductive system and breast disorders	Erectile dysfunction, testicular	Gynecomastia				

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
	atrophy, libido decreased					
General disorders and administration site conditions	Injection site reaction (e.g. induration, erythema, pain, abscess, swelling, nodules and necrosis), fatigue					

Pediatric Patients

In the initial phase of therapy, a short-term increase, also known as a 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.

Frequency / System	Very Common	Common	Uncommon	Rare	Very Rare	Not Known

Organ Class						
Immune system disorders					Hypersensitivity, anaphylactic reaction, rash, pruritus, urticaria, wheezing, fever and chills	
Nervous system disorders		Headache	Pseudotumor cerebri / idiopathic intracranial hypertension			
Gastrointestinal disorders		Abdominal pain, nausea, vomiting				
Skin and subcutaneous tissue disorders		Acne				
Musculoskeletal and connective tissue disorders						Myalgia

Reproductive system and breast disorders		Vaginal hemorrhage,** Vaginal discharge				
General disorders and administration site conditions		Injection site reaction (e.g. induration, erythema, pain, abscess, swelling, nodules and necrosis)				

**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. Pituitary suppression should then be determined by a luteinizing hormone-releasing hormone (LHRH) stimulation test.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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. 11.25 mg 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.

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)

5.2 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

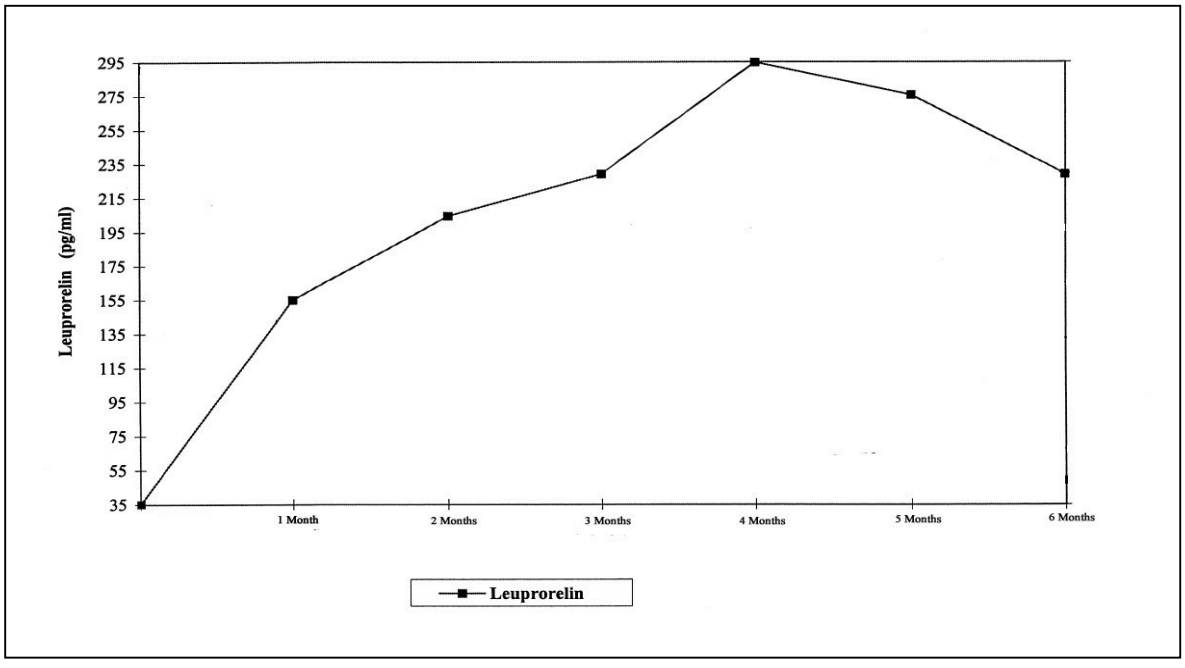
to maintenance levels in 7 to 14 days. *ENANTONE L.P. 11.25 mg* provides continuous plasma levels for up to 117 days resulting in suppression of testosterone to below castration level within 4 weeks of the first injection in the majority of patients.

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).

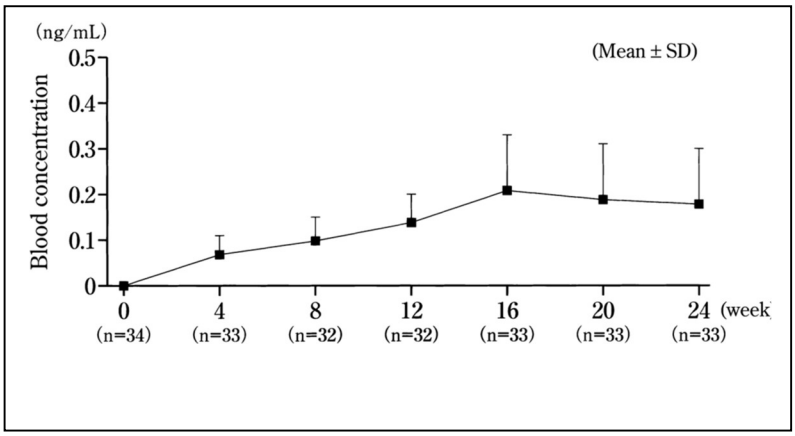
From the first injection, the leuprorelin serum levels increase reaching maximal serum levels at month 4 (294.79 pg/ml ± 105.42) and slightly decrease until month 6 (229.02 pg/ml ± 103.33).



<u>Figure 1</u>: 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.



5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polylactic acid, Mannitol, Methylene Chloride, Polyvinyl Alcohol, Carboxymethylcellulose Sodium, Polysorbate 80 and Water for injection

6.2 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.

6.3 Shelf life

See on carton package

6.4 Special precautions 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.

6.5 Nature and contents of container

Dual chamber pre-filled syringe (DPS) with a needle (23 G)

6.6 Special precautions for disposal and other handling

INSTRUCTIONS FOR USE

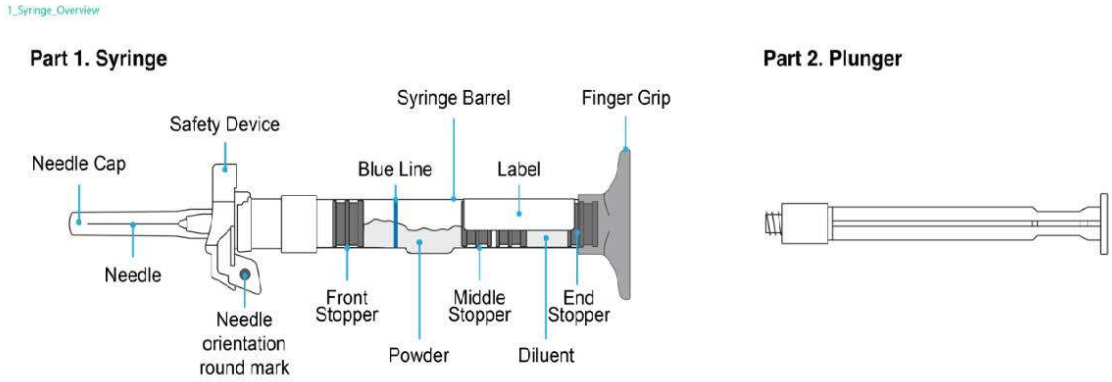
ENANTONE is supplied as a dual-chamber prefilled syringe for injection.

This Instructions for Use contains information on how to reconstitute and inject ENANTONE

Important Information:

- **Do not** use if medication is expired.
- **Do not** use if syringe or packaging appears damaged.
- **Do not** use the syringe if the powder appears clumped or caked.
- **Do not** use the syringe if the powder or diluent appears discolored.
- Storage Conditions:
- Keep the dual-chamber syringe in the outer carton in order to protect from light.
- Hold the syringe upright (with the needle side up) throughout entire preparation to prevent leakage. If leaking occurs, the dose should not be administered.
- Use immediately after mixing as the suspension settles out very quickly following reconstitution.
- This medication may be injected intramuscularly subcutaneously.

Parts Overview



The device may have the plunger already attached to the syringe.

Preparation

1. Wash hands before opening the syringe package. **(Figure 1)**

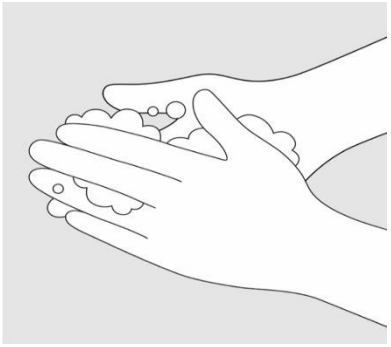


Figure 1: Wash hands Reconstitution

2. Open package and remove the syringe (Parts Overview Part 1). **(Figure 2)**

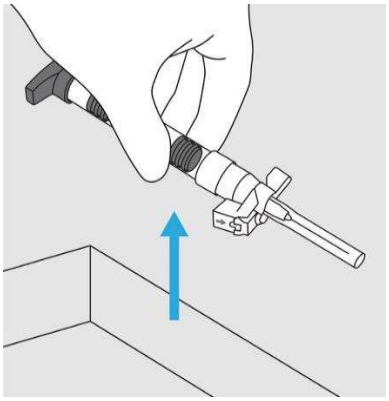


Figure 2: Remove Syringe

3. Check the expiration date printed on the syringe, and the powder and diluent in the syringe barrel. The powder should be white and dry, and the diluent should be clear.
4. Inspect the syringe for any damage. **(Figure 3)**

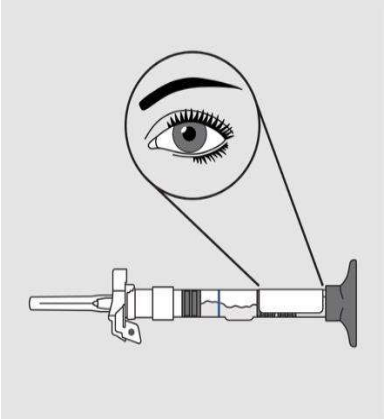


Figure 3: Inspect Syringe

a. **Do not** use the syringe if the expiration date has passed.
b. **Do not** use the syringe if the powder appears clumped or caked.
c. **Do not** use the syringe if powder or diluent appear discolored.
d. **Do not** use the syringe if any part of it is damaged.

5. Gently tap the syringe to remove any lumps and release any powder stuck on the syringe walls. **(Figure 4)**

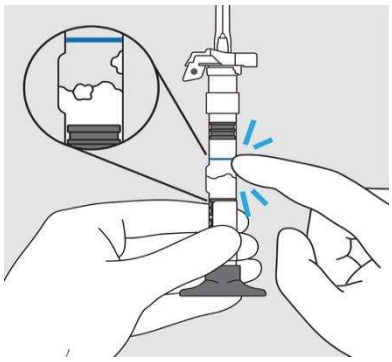


Figure 4: Check Powder

6. Remove the plunger (part 2) from the package. **(Figure 5)**

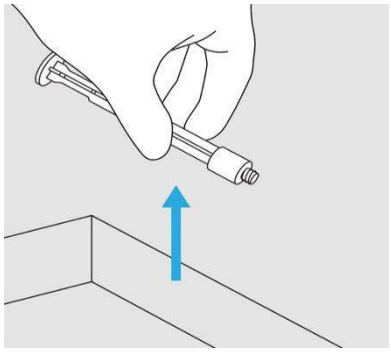


Figure 5: Remove plunger

7. Screw the plunger rod into the bottom of the syringe until the end stopper begins to rotate.

   (Figure 6)

   a. **Do not** twist or pull the plunger rod back once it has been attached.

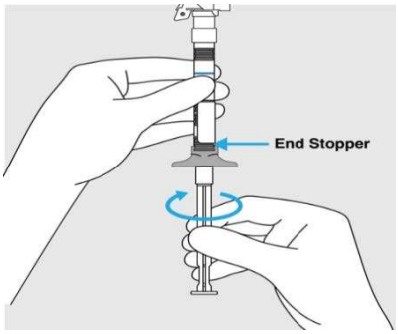


Figure 6: Screw in plunger rod

8. **Without removing the needle cap, twist the needle to the right (clockwise) to ensure it is secured tightly. (Figure 7)**
   a. **Do not** remove needle cap until you are ready to inject.

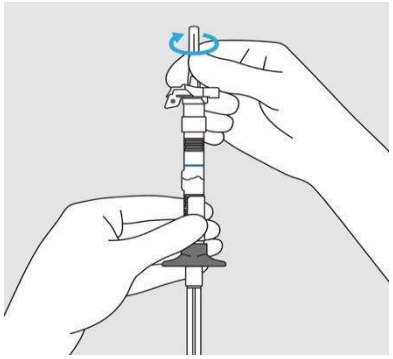


Figure 7: Twist needle to tighten

9. Holding the syringe upright, release the diluents by slowly pushing the plunger until the middle stopper reaches the blue line in the middle of the syringe. You should see the diluent flowing into the interior chamber above the blue line. (Figure 8)
   a. **Do not** remove the needle cap before releasing the diluent.
   b. **Do not** push the plunger too quickly or push past the blue line as these actions may cause leaking.
   c. **Do not** withdraw plunger again.

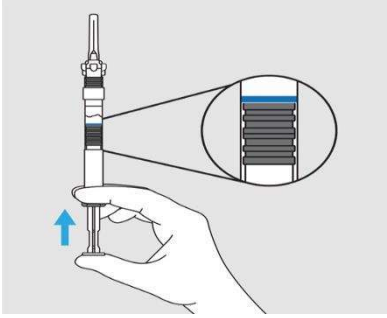


Figure 8: Release diluent

10. Gently tap the syringe against the palm of your hand to mix the powder and diluent until it forms a uniform suspension. When properly mixed, the suspension should appear milky with no visible lumps. (Figure 9)
    a. If particles stick to the stopper during mixing, dislodge them by gently tapping the syringe with your finger.
    b. Avoid hard tapping or shaking to prevent the generation of bubbles.
    c. Use immediately after mixing as the suspension settles out very quickly following reconstitution.

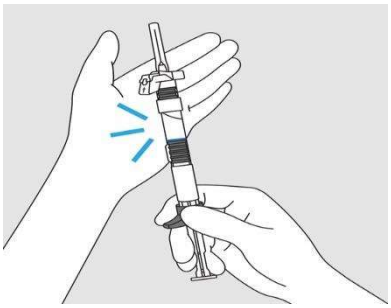


Figure 9: Tap syringe against palm to mix

11. Remove the needle cap by pulling it straight upwards. (Figure 10)
    a. **Do not** twist the needle cap.

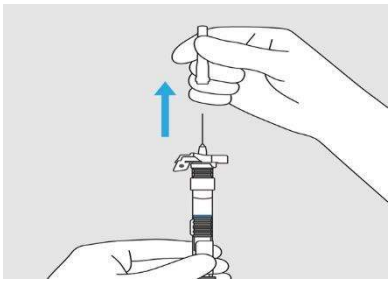


Figure 10: Pull upwards without twisting to remove needle cap

12. Prime the syringe by pushing the plunger upward until all air has been expelled from the syringe. (Figure 11)

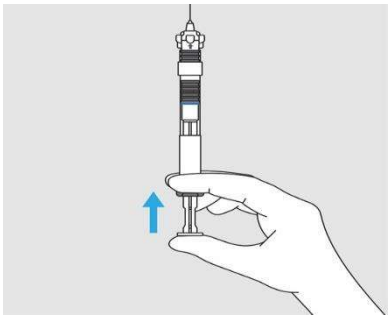


Figure 11: Push plunger to prime syringe

13. The syringe is now ready for injection. Use immediately as the suspension settles out very quickly following reconstitution.

Intramuscular Administration

1. Choose the injection site. Intramuscular injection sites include shoulder (deltoid), upper buttock (ventrogluteal), and thigh. (Figure 12)

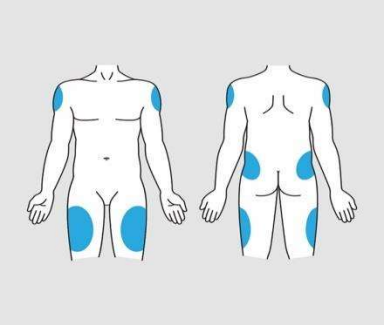


Figure 12: Intramuscular injection sites

2. Clean the skin at the injection site with an alcohol swab and allow to air-dry.
   a. **Do not** inject at a location where the skin is red, swollen, scarred, or damaged.
   b. **Do not** use the same injection site for more than one injection consecutively.
3. Gently pull the skin at the injection site taut and insert needle at a 90º or 180º angle. Before inserting the needle, check the orientation of the safety device. The arrow on the safety device should be pointed towards the patient, with the round mark directed upward. (Figure 13)

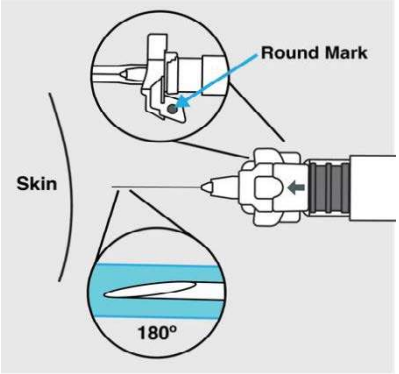


Figure 13: Pull skin taut and insert needle

4. Once the needle has been inserted, aspirate the needle by pulling the plunger backward for 5–10 seconds. Care should be taken to avoid inadvertent injection into a blood vessel. If blood is visible in the needle barrel, stop the injection and withdraw the needle immediately. (Figure 14)

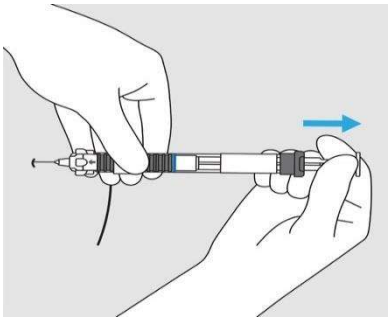


Figure 14: Pull plunger backward to aspirate

5. Push the plunger all the way down slowly until entire contents of the syringe have been injected. Pull needle straight out at the same angle it was inserted, then use clean gauze to apply gentle pressure. (Figure 15)
   a. **Do not** rub the injection site.
   b. **Do not** recap the needle after injection.

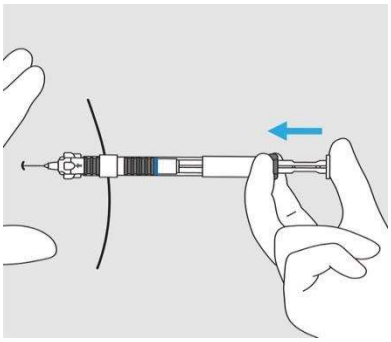


Figure 15: Push plunger to inject

6. When injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a “CLICK” is heard or felt and the needle is fully covered. (Figure 16)

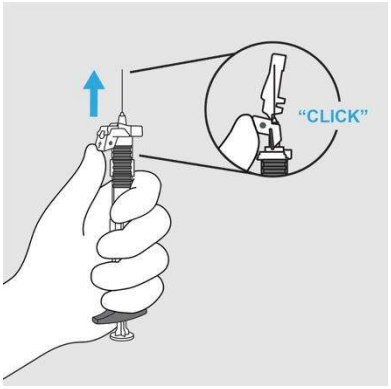


Figure 16: Activate safety device

Subcutaneous Administration

1. Choose the injection site. Subcutaneous injection sites include stomach area (abdomen), thighs, upper arms, and buttock. (Figure 12).
2. Clean the skin at the injection site with an alcohol swab and allow to air-dry.
    a. **Do not** inject at a location where the skin is red, swollen, scarred, or damaged.
    b. **Do not** use the same injection site for more than one injection consecutively.

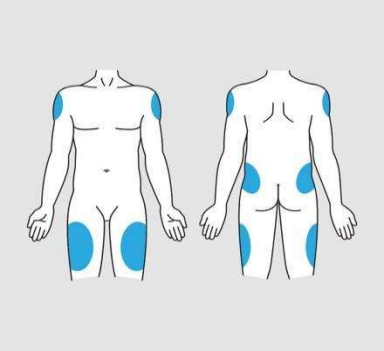


Figure 12: Subcutaneous injection sites

3. Pinch a 2.5cm section of skin between your fingers and insert needle at a 30º – 90º angle. Before inserting the needle, check the orientation of the safety device. The arrow on the safety device should be pointed towards the patient, with the round mark directed upward. (Figure 13)

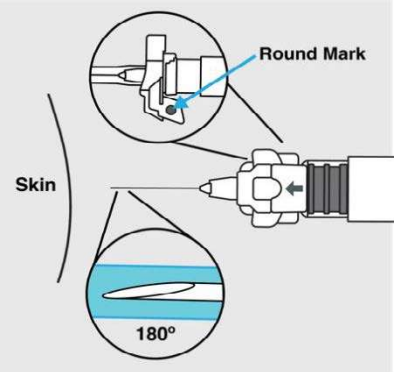


Figure 13: Pinch skin and insert needle

4. Push the plunger all the way down slowly until the entire contents of the syringe have been injected. Pull needle straight out at the same angle it was inserted, then use clean gauze to apply gentle pressure. (Figure 14)
    a. **Do not** rub the injection site.
    b. **Do not** recap the needle after injection.

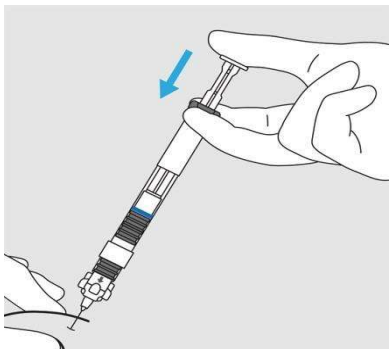


Figure 14: Push plunger to inject

5. When the injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a “CLICK” is heard or felt and the needle is fully covered. (Figure 15)

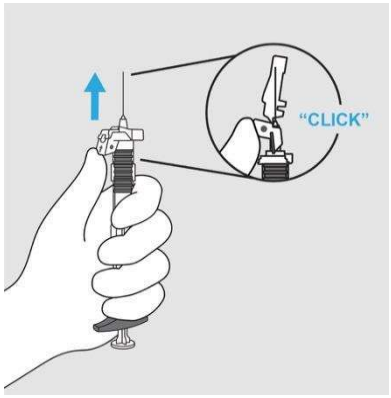


Figure 15: Activate safety device

Intramuscular and Subcutaneous Administration

1. Choose the injection site. Intramuscular injection sites include shoulder (deltoid), upper buttock (ventrogluteal), and thigh. (Figure 12) Subcutaneous injection sites include stomach area (abdomen), thighs, upper arms, and buttock. (Figure 13)
2. Clean the skin at the injection site with an alcohol swab and allow to air-dry.
    a. **Do not** inject at a location where the skin is red, swollen, scarred, or damaged.
    b. **Do not** use the same injection site for more than one injection consecutively.

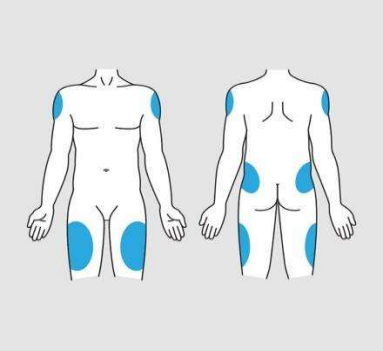


Figure 12: Intramuscular injection sites

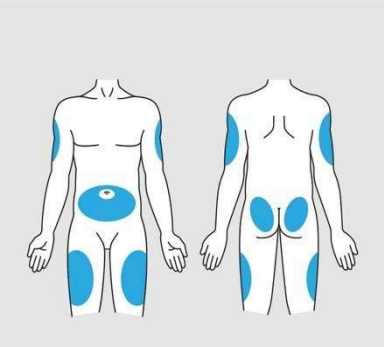


Figure 13: Subcutaneous injection sites

3. For intramuscular injection:
    a. Gently pull the skin at the injection site taut and insert needle at a 90º or 180º angle to the skin. Before inserting the needle, check the orientation of the safety device. The arrow on the safety device should be pointed towards the patient, with the round mark directed upward. **(Figure 14)**

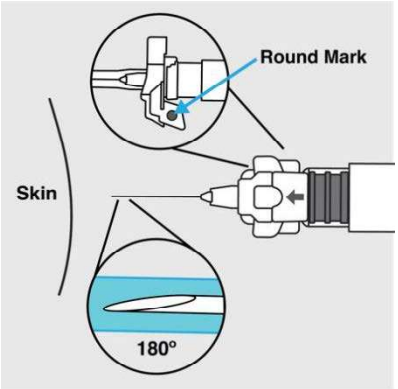


Figure 14: Pull skin taut and insert needle

b. Once the needle has been inserted, aspirate the needle by pulling the plunger backward for 5–10 seconds. Care should be taken to avoid inadvertent injection into a blood vessel. If blood is visible in the needle barrel, stop the injection and withdraw the needle immediately. **(Figure 15)**

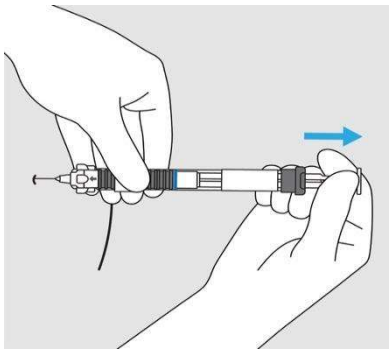


Figure 15: Pull plunger backward to aspirate

c. Push the plunger all the way down slowly until entire contents of the syringe have been injected. Pull needle straight out at the same angle it was inserted, then use clean gauze to apply gentle pressure. **(Figure 16)**

   i. **Do not** rub the injection site.

   ii. **Do not** recap the needle after injection.

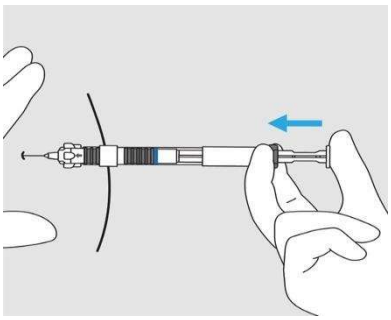


Figure 16: Push plunger to inject

d. When injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a "CLICK" is heard or felt and the needle is fully covered. **(Figure 16)**

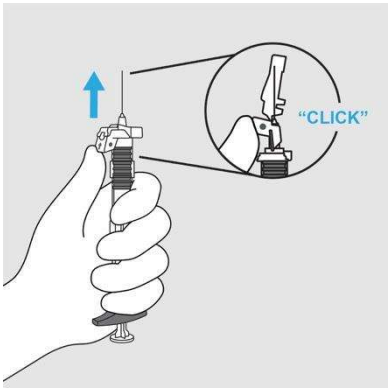


Figure 16: Activate safety device

4. For Subcutaneous Injection:

a. Pinch a 2.5cm section of skin between your fingers and insert needle at a 30º – 90º angle. Before inserting the needle, check the orientation of the safety device. The arrow on the safety device should be pointed towards the patient, with the round mark directed upward. **(Figure 17)**

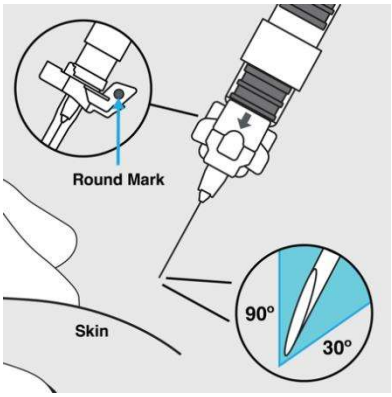


Figure 17: Pinch skin and insert needle

b. Push the plunger all the way down slowly until the entire contents of the syringe have been injected. Pull needle straight out at the same angle it was inserted, then use clean gauze to apply gentle pressure. (Figure 18)

   i. **Do not** rub the injection site.

   ii. **Do not** recap the needle after injection.

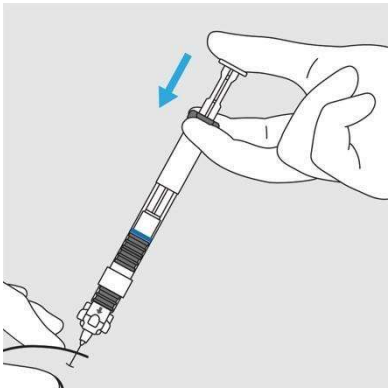


Figure 18: Push plunger to inject

c. When the injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a “CLICK” is heard or felt and the needle is fully covered. (Figure 19)

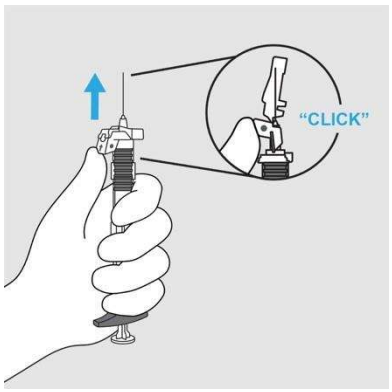


Figure 19: Activate safety device Storing

Disposing of ENANTONE

Dispose of the used device in the appropriate sharp's container in accordance with your local standard procedure.

7 Marketing authorization holder

Manufactured by: Takeda Pharmaceutical Company Limited, Hikari Plant, Yamaguchi, Japan

Or

Manufactured by: 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

8 Marketing authorization Numbers

Reg.No. 1C 132/47 (N)

9 Date of authorization

30 July 2004

10 Date of revision of the text

Nov 2024