SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ENANTONE L.P. 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Advanced Prostate Cancer

4.2 Posology and method of 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**

- 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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.

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).

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.

4.5 Interaction with the other medicinal products and other forms of interactions

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).

4.6 Pregnancy, Lactation and Fertility

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.

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 ($\geq$ 1/10); common ($\geq$ 1/100 to < 1/10); uncommon ($\geq$ 1/1,000 to < 1/100); rare ($\geq$ 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	Mood changes (short term			

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
		(long term use of leuprorelin)	use of leuprorelin)			
Nervous system disorders					Pituitary apoplexy (following initial administration in patients with pituitary adenoma), pituitary hemorrhage1	Seizure
Skin and subcutaneous tissue disorders						Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema multiforme, Bullous dermatitis, Exfoliative

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

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Metabolism and nutrition disorders						Metabolic syndrome (including hypertension, dyslipidemia, insulin resistance, abnormal glucose tolerance)
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 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	Dizziness1			
Eye disorders						Visual impairment
Cardiac disorders						Palpitations,1 QT prolongation (see Special Warnings and Special Precautions for Use, 4.4 and

Frequency / System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
						Interaction with Other Medications and Other Forms of Interaction, 4.5)
Gastrointestinal disorders		Nausea	Vomiting, 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	Erectile	Gynecomastia				

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

4.9 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

5 PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 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.

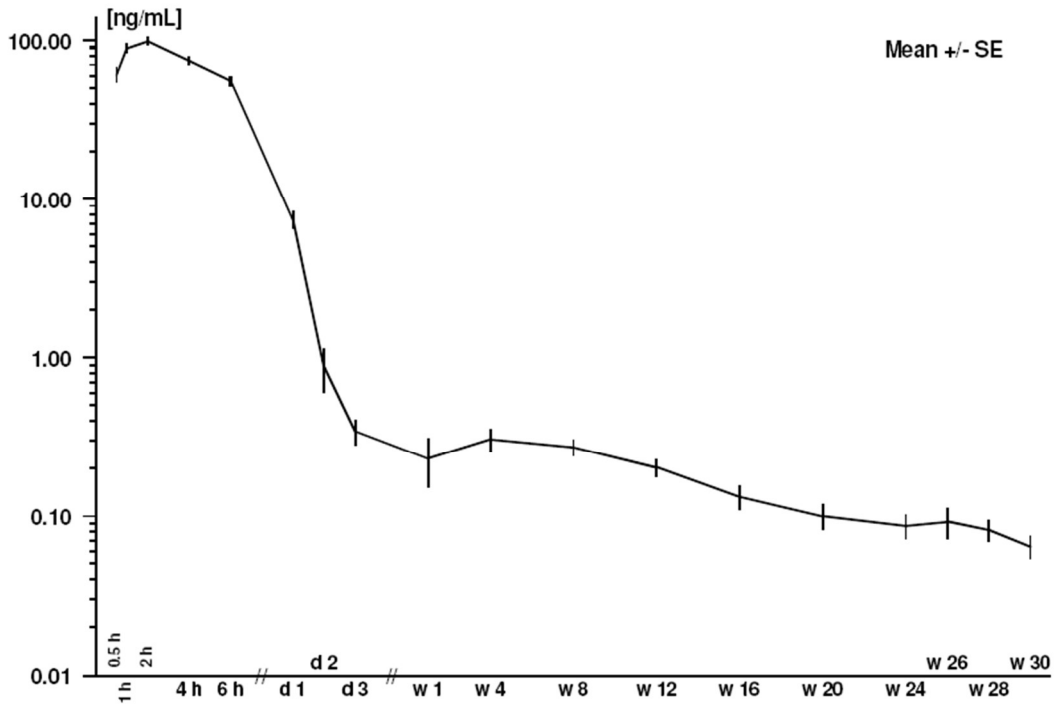


Fig. 1: Leuprorelin serum levels after a single s.c. administration of 30.0 mg leuprorelin acteate as *ENANTONE L.P. 30 mg*.

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

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PLA(6M), Mannitol, Water for injections, Methylene Chloride, Polyvinyl Alcohol, Acetic Acid, Glacial, CMC-Na, Polysorbate 80 and Nitrogen

6.2 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.

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 (23G)

6.6 Special precautions for disposal and other handling

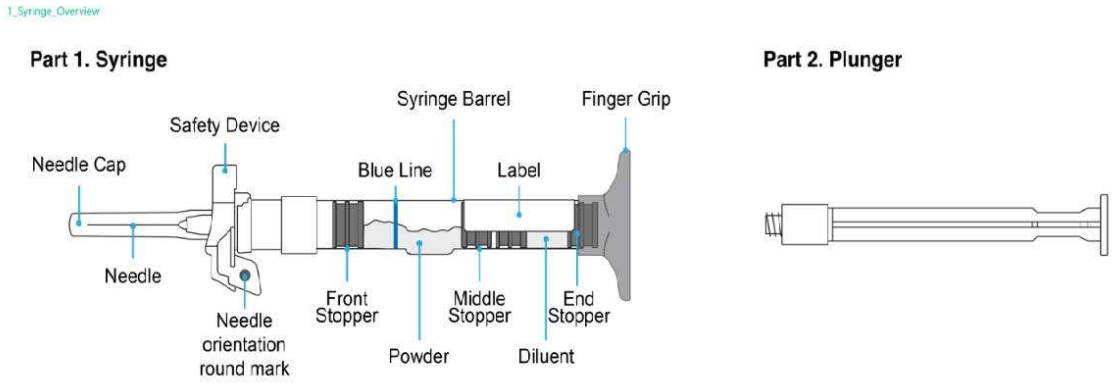
INSTRUCTIONS FOR USE

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

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)

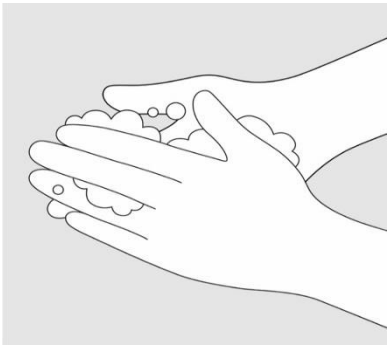


Figure 1: Wash hands Reconstitution

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

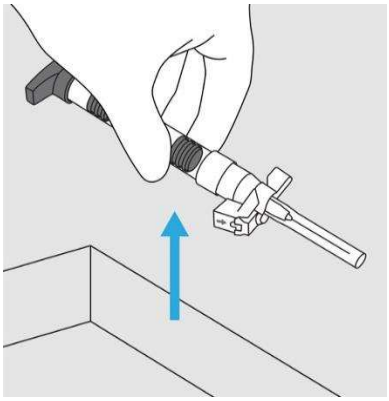


Figure 2: Remove Syringe

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)

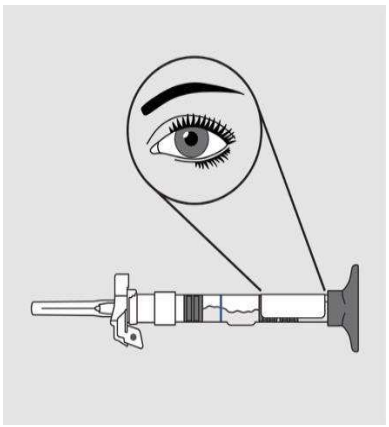


Figure 3: Inspect Syringe

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)

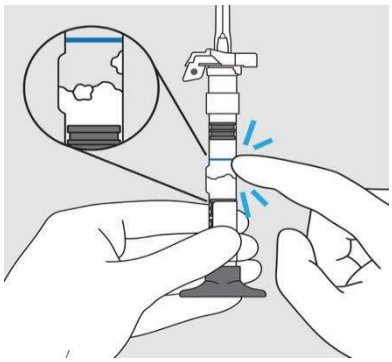


Figure 4: Check Powder

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

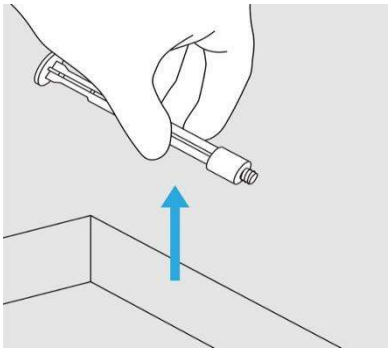


Figure 5: Remove plunger

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.

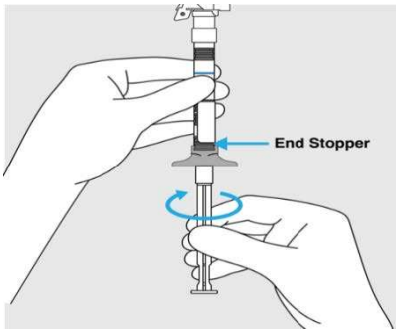


Figure 6: Screw in plunger rod

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.

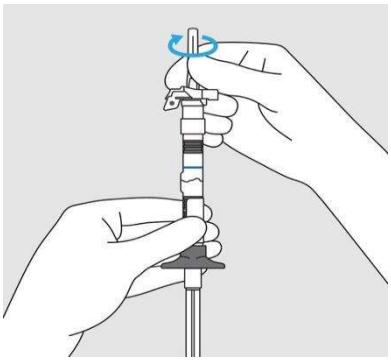


Figure 7: Twist needle to tighten

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.

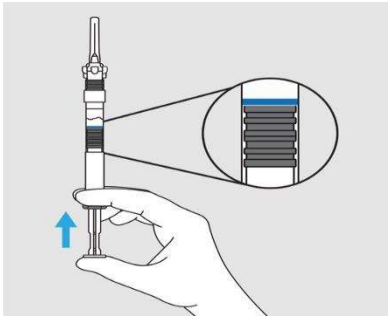


Figure 8: Release diluent

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.

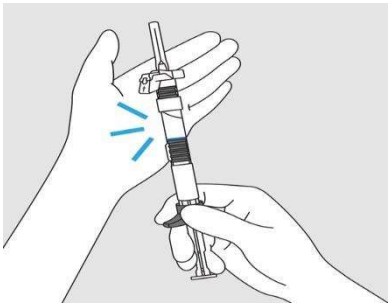


Figure 9: Tap syringe against palm to mix

11. Remove the needle cap by pulling it straight upwards. (Figure 10)

    a. **Do not** twist the needle cap.

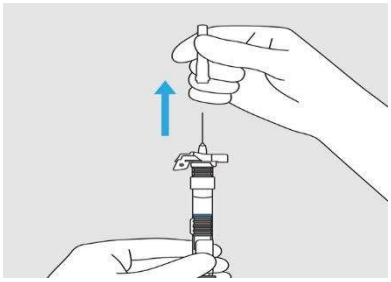


Figure 10: Pull upwards without twisting to remove needle cap

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

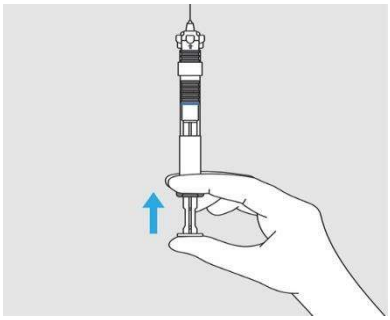


Figure 11: Push plunger to prime syringe

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)

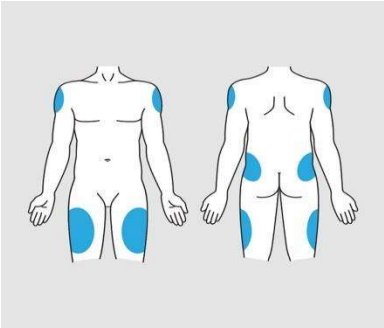


Figure 12: Intramuscular injection sites

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)

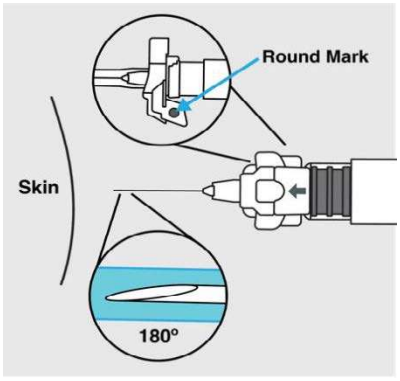


Figure 13: Pull skin taut and insert needle

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)

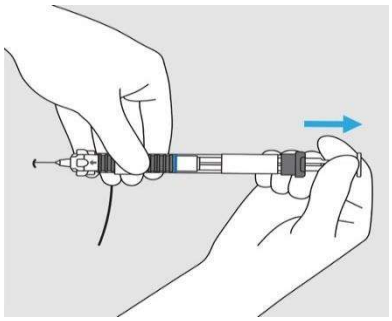


Figure 14: Pull plunger backward to aspirate

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.

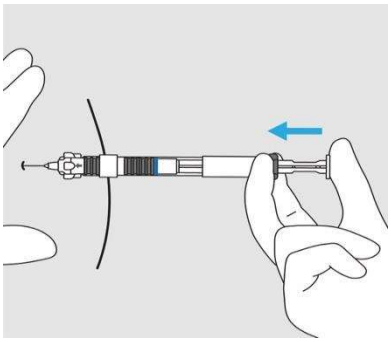


Figure 15: Push plunger to inject

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)

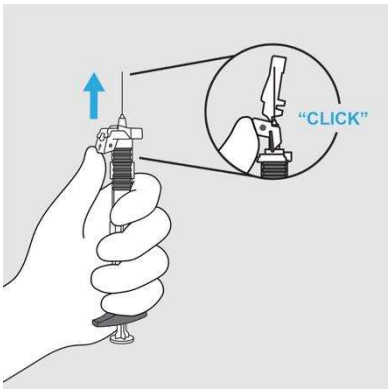


Figure 16: Activate safety device

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.

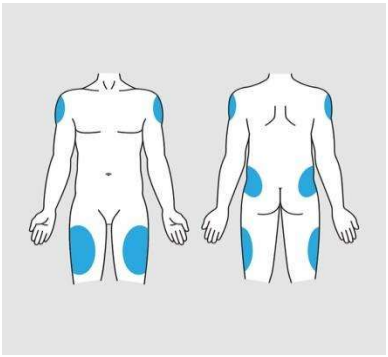


Figure 12: Subcutaneous injection sites

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)

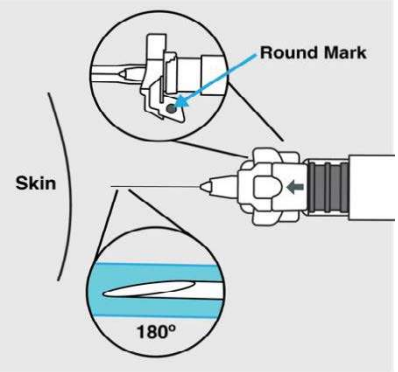


Figure 13: Pinch skin and insert needle

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.

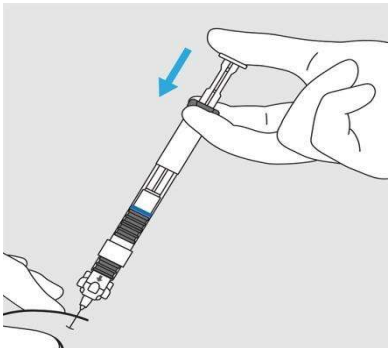


Figure 14: Push plunger to inject

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)

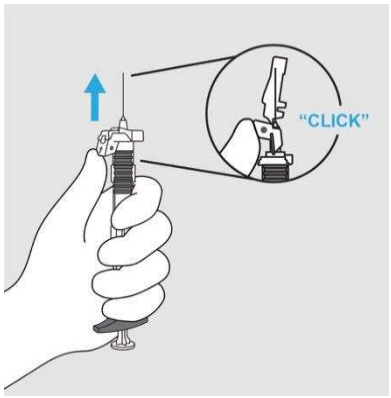


Figure 15: Activate safety device

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.

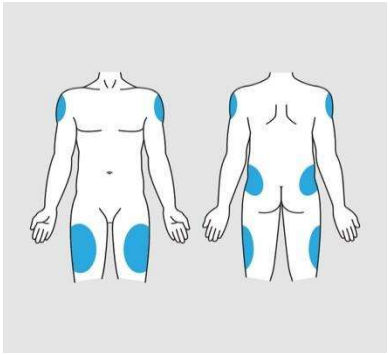


Figure 12: Intramuscular injection sites

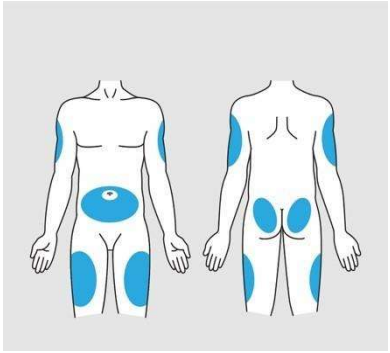


Figure 13: Subcutaneous injection sites

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)**

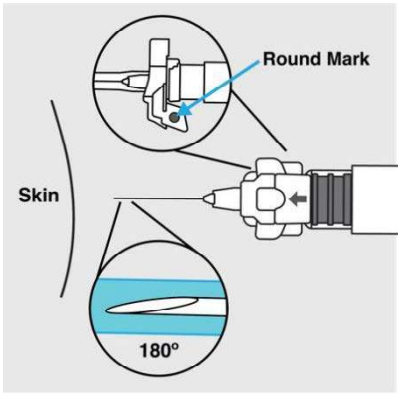


Figure 14: Pull skin taut and insert needle

   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)**

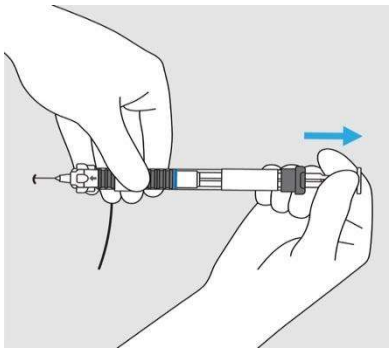


Figure 15: Pull plunger backward to aspirate

   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.

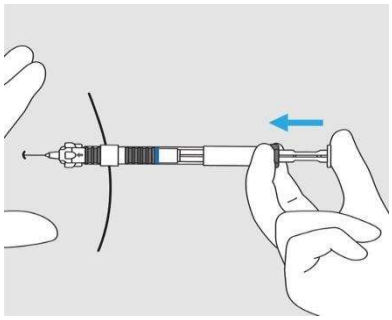


Figure 16: Push plunger to inject

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)**

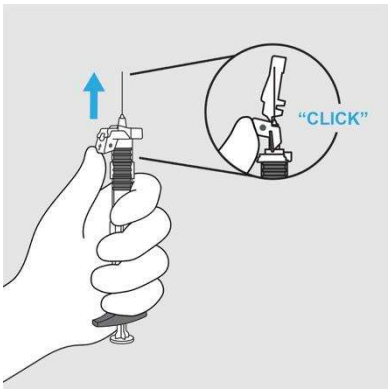


Figure 16: Activate safety device

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)**

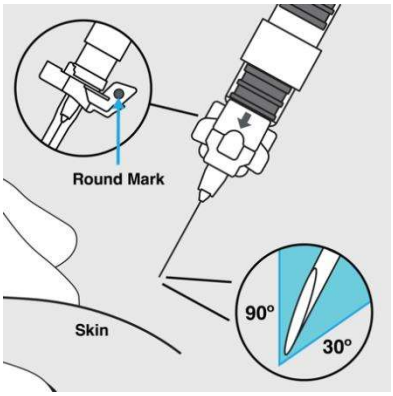


Figure 17: Pinch skin and insert needle

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.

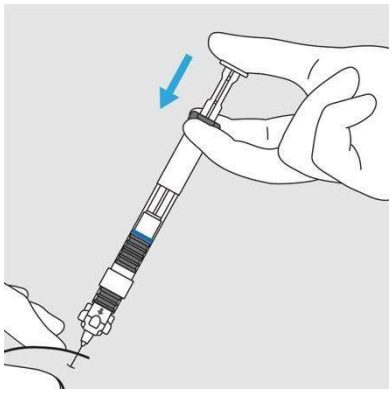


Figure 18: Push plunger to inject

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)**

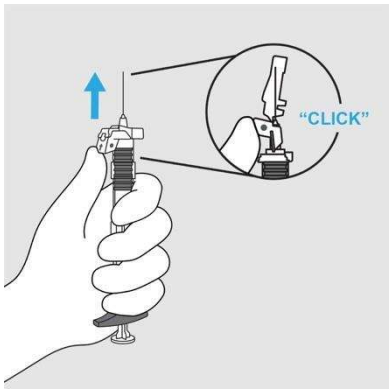


Figure 19: Activate safety device Storing

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, Osaka, Japan
Packed and Released by: Takeda Pharmaceutical Company Limited, Hikari-city, Yamaguchi, Japan
Imported by: Takeda (Thailand), Ltd., Bangkok, Thailand

8 MARKETING AUTHORIZATION NUMBERS

Reg. No. 1C 12/66 (NC)

9 DATE OF AUTHORIZATON

30 Jun 2023

10 DATE OF REVISON OF THE TEXT

Nov 2024