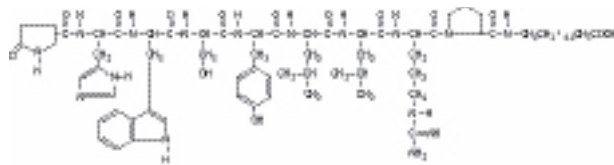




**DESCRIPTION**

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Leuprolide acetate injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing 5 mg/mL of leuprolide acetate, 6.3 mg/mL sodium chloride, USP for tonicity adjustment, 9 mg/mL of benzyl alcohol as a preservative and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

**CLINICAL PHARMACOLOGY**

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

**Pharmacokinetics**

*Absorption*

Bioavailability by subcutaneous administration is comparable to that by intravenous administration.

*Distribution*

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

*Metabolism*

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of 14C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

*Excretion*

Following administration of leuprolide acetate for depot suspension 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

*Special Populations*

The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

*Drug Interactions*

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

**Clinical Studies**

In a controlled study comparing leuprolide acetate injection 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years of treatment. The objective response to treatment was also similar for the two groups.

**INDICATIONS AND USAGE**

Leuprolide acetate injection is indicated in the palliative treatment of advanced prostatic cancer.

**CONTRAINDICATIONS**

Leuprolide acetate injection is contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs or any of the excipients in leuprolide acetate injection. Reports of anaphylactic reactions to synthetic GnRH (Factrel) or GnRH agonist analogs have been reported in the medical literature.<sup>1</sup>

Leuprolide acetate injection is contraindicated in women who are or may become pregnant while receiving the drug. Leuprolide acetate injection may cause fetal harm when administered to a pregnant woman.

**WARNINGS**

Initially, leuprolide acetate injection, like other LH-RH agonists, causes increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of leuprolide acetate injection treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Periodic monitoring of serum testosterone and PSA levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

**PRECAUTIONS**

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** and **ADVERSE REACTIONS** section).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

**Information For Patients**

See **INFORMATION FOR PATIENTS** which appears after the **REFERENCE** section.

**Laboratory Tests**

Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

**Drug Interactions**

None have been reported. (see **CLINICAL PHARMACOLOGY – Pharmacokinetics**).

**Drug/Laboratory Test Interactions**

Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

**Pregnancy, Teratogenic Effects**

Pregnancy Category X. (see **CONTRAINDICATIONS** section). When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, leuprolide acetate injection produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in major fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate injection in rabbits and with the highest dose in rats. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of leuprolide acetate injection, the patient should be apprised of the potential hazard to the fetus.

**Nursing Mothers**

It is not known whether leuprolide acetate is excreted in human milk. Leuprolide acetate injection should not be used by nursing mothers.

**Pediatric Use**

See labeling for Leuprolide Acetate Injection for Pediatric Use for the safety and effectiveness in children with central precocious puberty.

**Geriatric Use**

In the clinical trials for leuprolide acetate injection, the majority (69%) of subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of leuprolide acetate injection in this population.

**ADVERSE REACTIONS**

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain. (See **WARNINGS** section.) In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurologic problems or increase the obstruction.

In a comparative trial of leuprolide acetate injection versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LEUPROLIDE ACETATE INJECTION (N=98)	DES (N=101)
	Number of Reports	
<b>Cardiovascular System</b>		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
<b>Gastrointestinal System</b>		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
<b>Endocrine System</b>		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
<b>Hemic and Lymphatic System</b>		
Anemia	5	5
<b>Musculoskeletal System</b>		
Bone pain	5	2
Myalgia	3	9
<b>Central/Peripheral Nervous System</b>		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
<b>Respiratory System</b>		
Dyspnea	2	8
Sinus congestion	5	6
<b>Integumentary System</b>		
Dermatitis	5	8
<b>Urogenital System</b>		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
<b>Miscellaneous</b>		
Asthenia	10	10

\*Physiologic effect of decreased testosterone.

In this same study, the following adverse reactions were reported in less than 5% of the patients on leuprolide acetate injection.

*Cardiovascular System*-Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*-Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System*-Libido decrease, Thyroid enlargement; *Musculoskeletal System* -Joint pain; *Central/Peripheral Nervous System*-Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*-Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*-Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*-Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*-Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

The following additional adverse reactions have been reported with leuprolide acetate injection or leuprolide acetate for depot suspension during other clinical trials and/or during postmarketing surveillance. Reactions considered as nondrug related by the treating physician are excluded.

*Cardiovascular System*-Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*-Hepatic dysfunction; *Endocrine System*-Libido increase; *Hemic And Lymphatic System*-Decreased WBC, Hemoptysis; *Musculoskeletal System*-Ankylosing spondylitis, Pelvic fibrosis; *Central/Peripheral Nervous System*-Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System*-Pulmonary infiltrate, Respiratory disorders; *Integumentary System*-Hair growth; *Urogenital System*-Penile swelling, Prostate pain; *Miscellaneous*-Hypoproteinemia, Hard nodule in throat, Weight gain, Increased uric acid.

*Changes in Bone Density*-Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

**OVERDOSAGE**

In rats, subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

**DOSAGE AND ADMINISTRATION**

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically. Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

**NOTE:** As with all parenteral products, inspect the solution for discoloration and particulate matter before each use.

**HOW SUPPLIED**

Leuprolide Acetate Injection is a sterile solution, supplied as follows:

NDC Number	Strength	Package
0703-4014-18	1 mg/0.2 mL	2.8 mL Multiple Dose Vial One multiple-dose vial per one 14-Day Patient Administration Kit

Store below 25°C (77° F). DO NOT FREEZE. Protect from light. Store vial in carton until contents are used.

Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

**REFERENCES**

- MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500-502.

**INFORMATION FOR PATIENTS**

NOTE: Be sure to consult your physician with any questions you may have or for information about leuprolide acetate injection and its use.

**What is leuprolide acetate injection?**

Leuprolide acetate injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH) a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones.

However, when you inject leuprolide acetate injection, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

Leuprolide acetate injection must be injected because, like insulin which is injected by diabetics, leuprolide acetate injection is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

**DIRECTIONS FOR USING LEUPROLIDE ACETATE INJECTION**

- Wash hands thoroughly with soap and water.
- If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use leuprolide acetate injection. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
- Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 mL or 20 unit mark.
- Take cover off needle. Push the needle through the center of the rubber stopper on the leuprolide acetate injection bottle.
- Push the plunger all the way in to inject air into the bottle.
- Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 mL or 20 unit mark.
- Toward the end of a two-week period, the amount of leuprolide acetate injection left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
- Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger slowly in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 mL or 20 unit mark.
- Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
- To protect your skin, inject each daily dose at a different body spot.
- Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
- Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
- Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle.
- Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
- Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

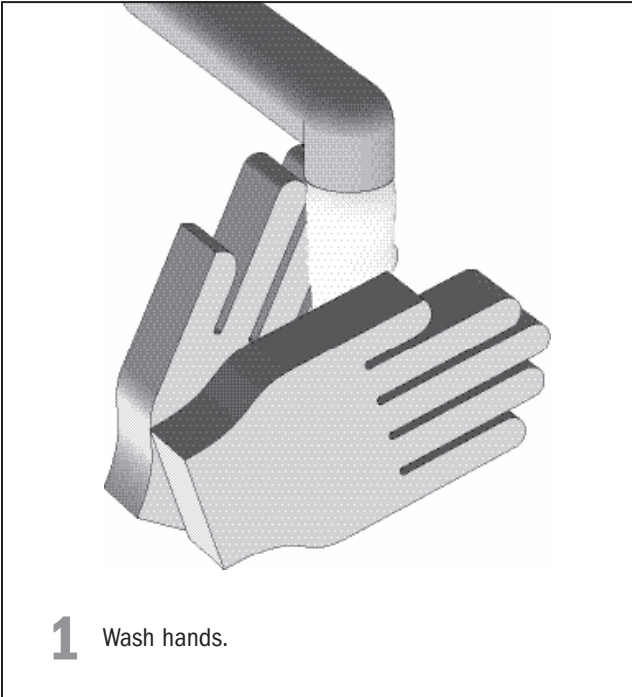
**SOME SPECIAL ADVICE**

- You may experience hot flashes when using leuprolide acetate injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor. Like other treatment options, leuprolide acetate injection may cause impotence. Notify your doctor if you develop new or worsened symptoms after beginning leuprolide acetate injection treatment.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- If you have experienced an allergic reaction to other drugs like leuprolide acetate injection, you should not use this drug.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure leuprolide acetate injection keeps working for you.
- If you need to use an alternate to the syringe supplied with leuprolide acetate injection, insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need leuprolide acetate injection so it will be at the pharmacy when you need it.
- Store below 25°C (77°F). Do not store near a radiator or other very warm place. Do not freeze. Protect from light – store vial in carton until use.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

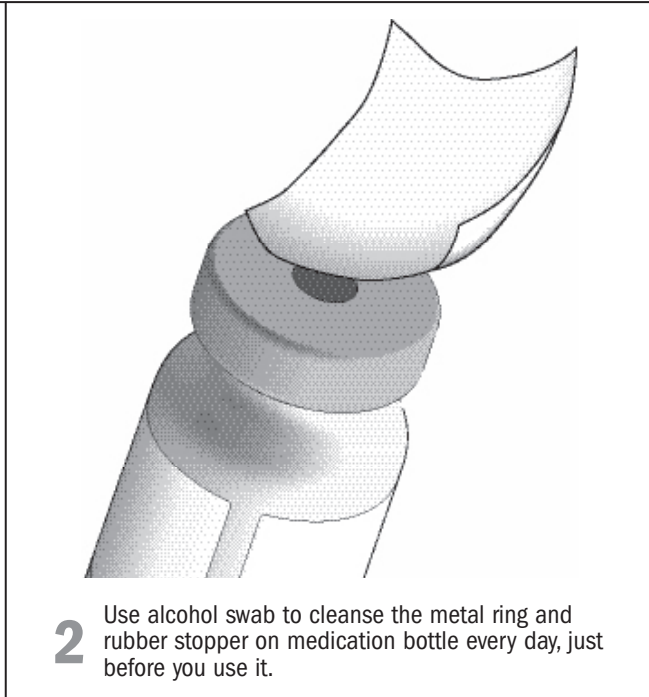


# Administering the Injection

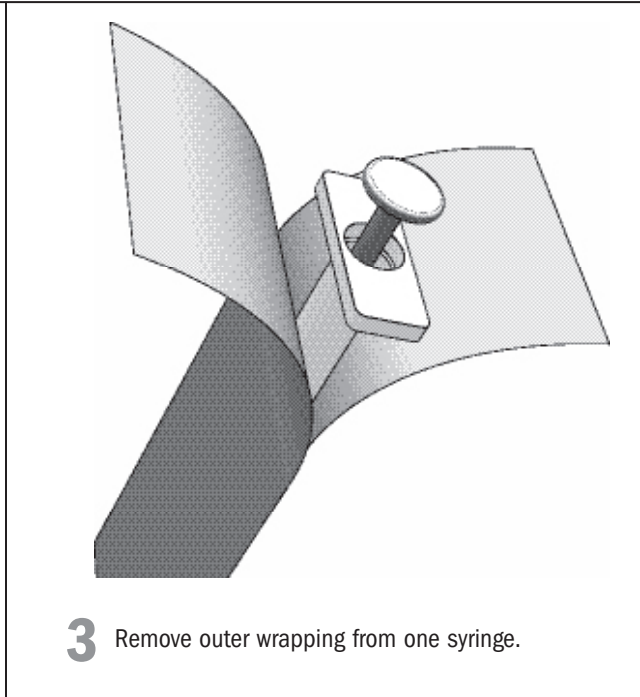
**Read this booklet before injecting medication.  
Read the complete instructions for injection.**



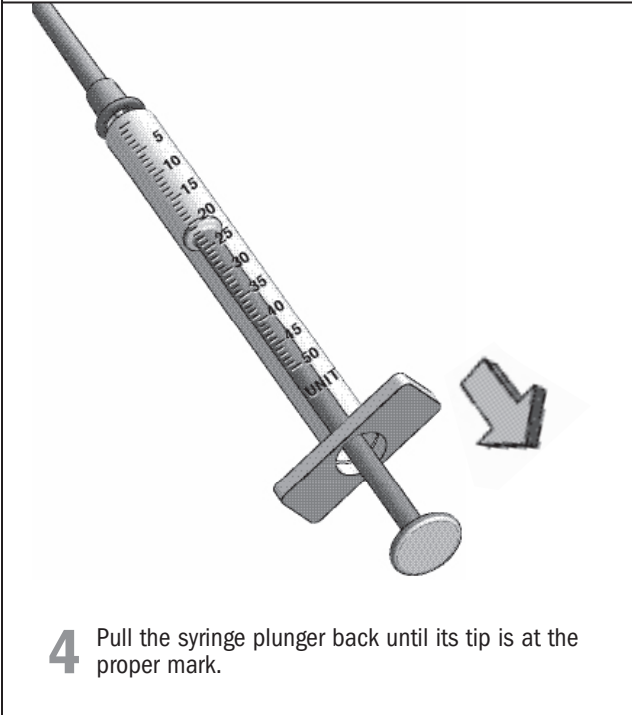
**1** Wash hands.



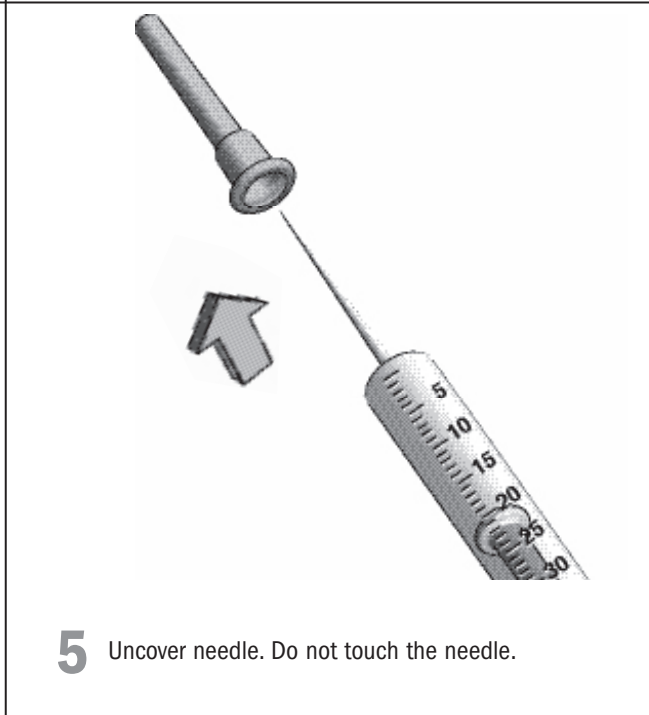
**2** Use alcohol swab to cleanse the metal ring and rubber stopper on medication bottle every day, just before you use it.



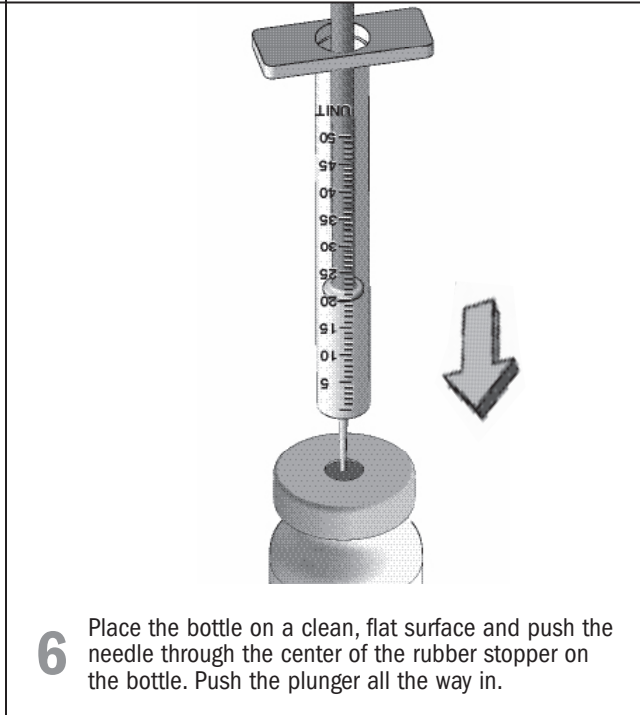
**3** Remove outer wrapping from one syringe.



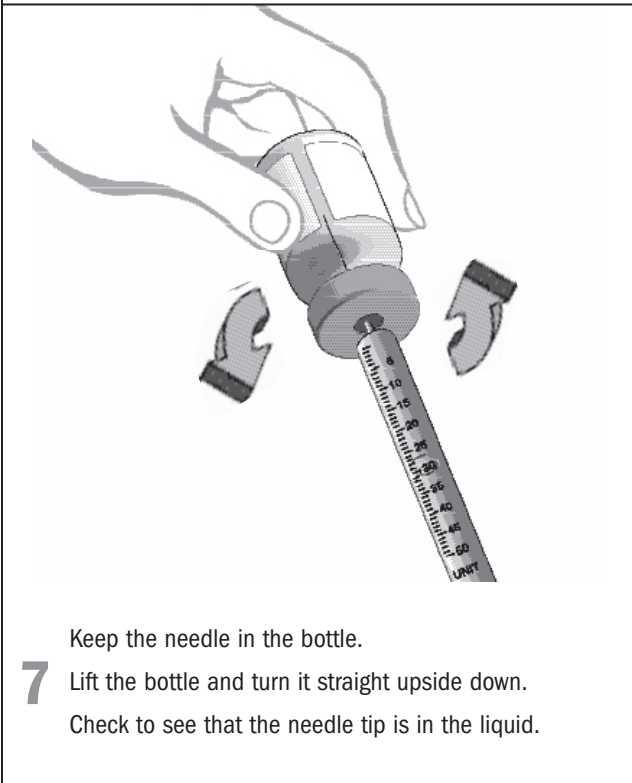
**4** Pull the syringe plunger back until its tip is at the proper mark.



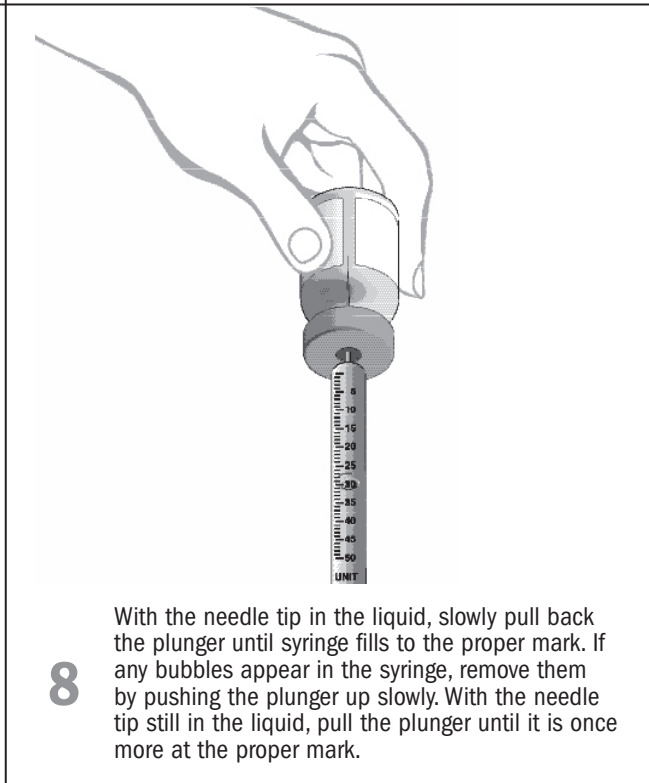
**5** Uncover needle. Do not touch the needle.



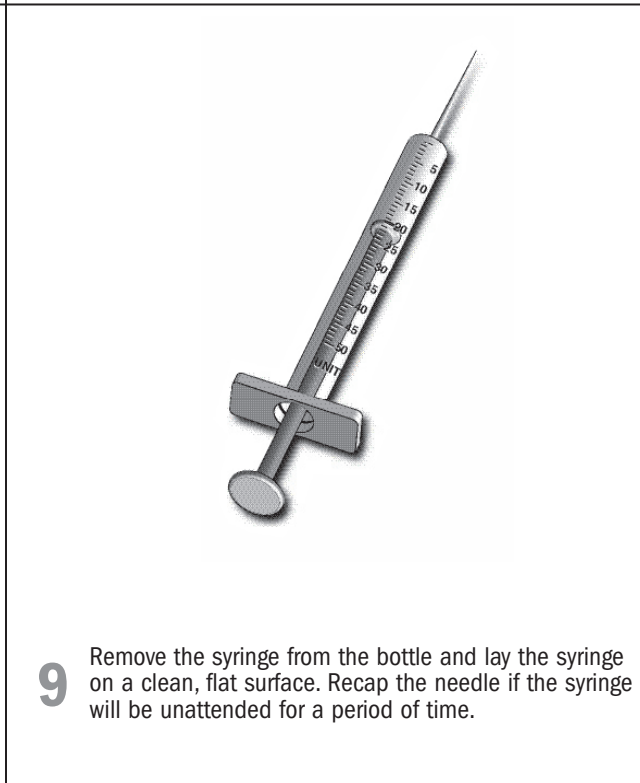
**6** Place the bottle on a clean, flat surface and push the needle through the center of the rubber stopper on the bottle. Push the plunger all the way in.



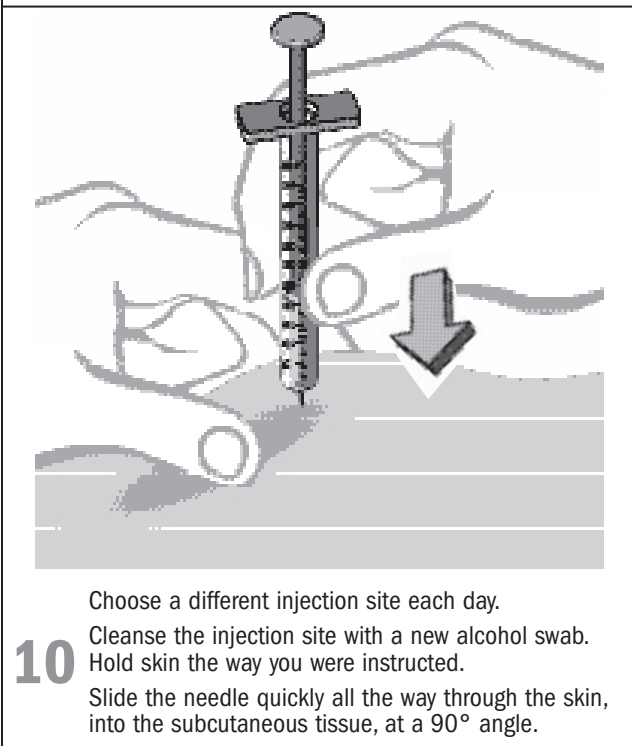
**7** Keep the needle in the bottle. Lift the bottle and turn it straight upside down. Check to see that the needle tip is in the liquid.



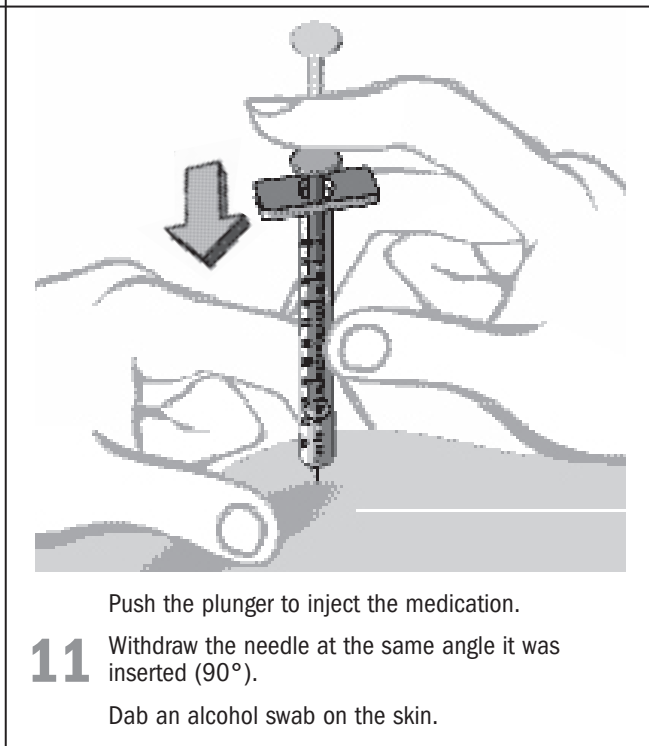
**8** With the needle tip in the liquid, slowly pull back the plunger until syringe fills to the proper mark. If any bubbles appear in the syringe, remove them by pushing the plunger up slowly. With the needle tip still in the liquid, pull the plunger until it is once more at the proper mark.



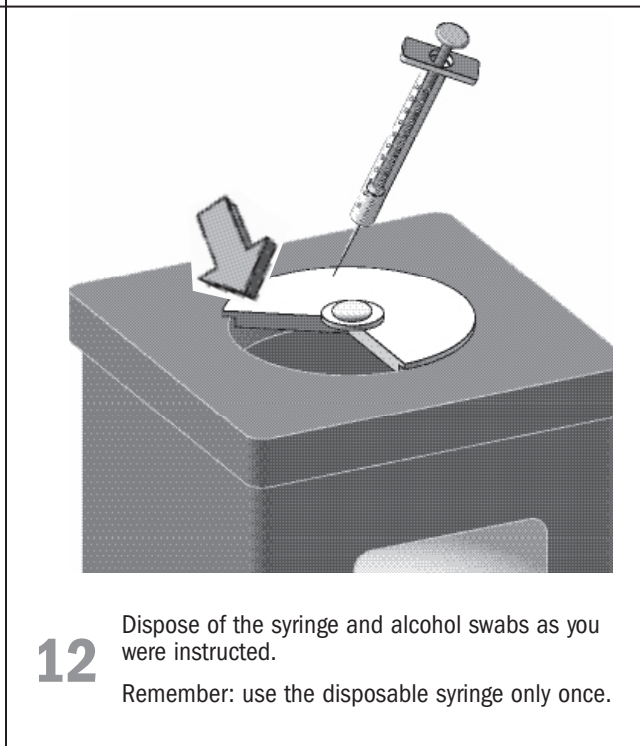
**9** Remove the syringe from the bottle and lay the syringe on a clean, flat surface. Recap the needle if the syringe will be unattended for a period of time.



**10** Choose a different injection site each day. Cleanse the injection site with a new alcohol swab. Hold skin the way you were instructed. Slide the needle quickly all the way through the skin, into the subcutaneous tissue, at a 90° angle.



**11** Push the plunger to inject the medication. Withdraw the needle at the same angle it was inserted (90°). Dab an alcohol swab on the skin.



**12** Dispose of the syringe and alcohol swabs as you were instructed. Remember: use the disposable syringe only once.